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Research article

Optimal treatment strategy of cancers with intratumor heterogeneity

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Abstract: Intratumor heterogeneity hinders the success of anti-cancer treatment due to the interaction between different types of cells. To recapitulate the communication of different types of cells, we developed a mathematical model to study the dynamic interaction between normal, drug-sensitive and drug-resistant cells in response to cancer treatment. Based on the proposed model, we first study the analytical conclusions, namely the nonnegativity and boundedness of solutions, and the existence and stability of steady states. Furthermore, to investigate the optimal treatment that minimizes both the cancer cells count and the total dose of drugs, we apply the Pontryagin's maximum(or minimum) principle (PMP) to explore the combination therapy strategy with either quadratic control or linear control functionals. We establish the existence and uniqueness of the quadratic control problem, and apply the forward-backward sweep method (FBSM) to solve the optimal control problems and obtain the optimal therapy scheme.

Keywords: mathematical oncology; drug resistance; heterogeneity; optimal control

1. Introduction

Intratumor heterogeneity contributes to the emergence of therapy resistance, which plays a vital role in cancer relapse. Biologically, heterogeneity may originate from cellular genetic and epigenetic modifications as well as the environmental changes [1, 2]. Clinically, adaptive responses to targeted therapies can facilitate both the expansion of pre-existing drug-resistant subpopulations and the acquisition of new mutations, which yields heterogeneity [2–4]. However, the dynamics of how intratumor heterogeneity may affect tumor evolution is not well understood, and is important for us to understand the mechanisms of drug resistance in cancer therapy.

There are mounting evidences that mutation can create favorable conditions for heterogeneity and result in cancer therapy resistance. A critical question arises that whether mutation is prior to or after the onset of therapy. Experiments have showed that mutations in *KRAS*, *TP53*, *ABL* or *MET* can

pre-exist before the initiation of therapy, and contribute to the development of drug resistance [5–10]. In addition, it is shown that mutations can also emerge in response to treatment stress and promote drug resistance [11–16]. The two mechanisms may imply different dynamics of cancer relapse, and quantitative studies are necessary to uncover the process of how mutation may affect treatment resistance over time.

Many mathematical models have been developed to study the complex dynamics of cancer resistance/recurrence [17–24]. For example, various ordinary differential equations models were developed to describe how the interaction between drug-sensitive and drug-resistant cancer cells may shape the progression of drug resistance [17–20]. Moreover, the interaction between cancer cells and stroma [21] or immune cells [22–24] are considered in different types of models. In addition to the tumor cells, the competition between normal cells and tumor cells can be important for tumor progression [25, 26]. Most existing models consider the tumor progression dynamics with pre-existing resistant cells, which interact with sensitive tumor cells through the competition in resources. Nevertheless, resistance cells can also be induced by the treatment behavior, by which sensitive cells can transit to resistant cells due to treatment stress. The mechanism of cell plasticity induced drug resistance is important clinically, however, to our knowledge, is not well studied quantitatively.

In recent years, the idea of adaptive therapy has attracted the attention of many researchers, and the mathematical tool of optimal control theory was applied to obtain the optimal therapy schemes in adaptive therapy. For example, from the standpoint of optimal control, minimization of the total drug count was analyzed in order to control IgG multiple myeloma [27]. The optimal control method was utilized in treatments of various types of cancers, including metastatic prostate cancer [17], immunotherapeutic treatment [28, 29], chemotherapy [30], combination of chemotherapy and stem cell transplants for acute myeloid leukemia [31], combination therapy of chronic myeloid leukemia [32], combination chemotherapy of antiangiogenic treatment [33], and bone metastasis treatment [34]. In these studies, the effects of cell plasticity induced drug resistance and the competition between tumor cells and normal cells are not included. Here, we ask how optimal control theory can help us to determine the optimal therapy strategy when both effects of the cell plasticity and competitions are considered.

In this study, to have a better understanding of tumor progression in the base of competitions between normal cells and various types of cancer cells, we develop a mathematical model that includes normal cells, drug-sensitive tumor cells and drug-resistant tumor cells, and apply the model to study the dynamics of tumor progression and treatment responses. First, mathematically, we consider the nonnegativity and boundedness of the model solutions, and the existence and stability of steady states. Next, applying the Pontryagin's maximum(or minimum) principle (PMP) [35], we derive the optimal treatment schedule that can minimize the tumor burden during the treatment and the total drug dose of combination therapy. Two types of optimal control problems are considered with different designations of cost functionals, including the quadratic and linear drug control, respectively.

2. Model formulation

To model the interaction between normal and tumor cells, we consider a mathematical model of tumor progression dynamics that includes normal cells, drug-sensitive and drug-resistant tumor cells (Figure 1). In the model, each type of cells proliferate with different rates that are dependent on the cell numbers and the microenvironmental cytokines regulating the cell proliferation pathway, and are removed due to cell death. All cells can secrete cytokines to regulate the proliferation of all cells, which form the competition between different types of cells. To consider the occurrence of mutation induced

by treatment stress, we assume a possible transition from drug-sensitive to drug-resistant cells.

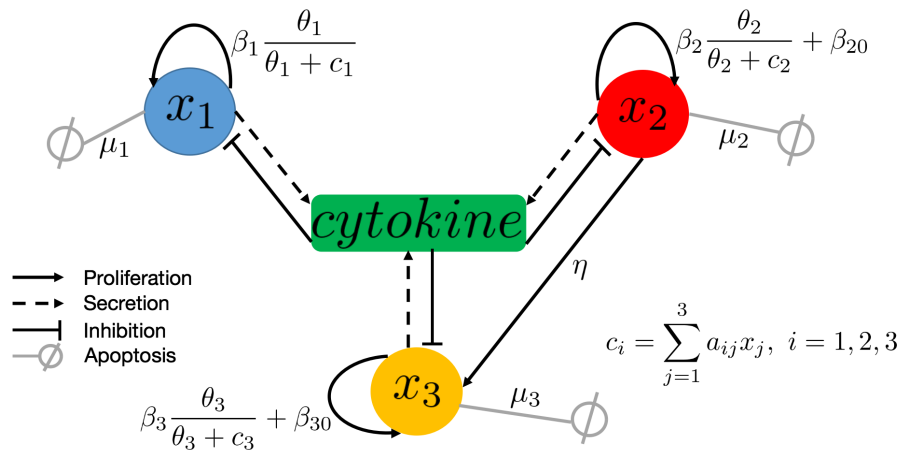

Figure 1. Schematic of the proposed model. There are three types of cells, including normal cells ($x_1(t)$), drug-sensitive ($x_2(t)$) and drug-resistant ($x_3(t)$) tumor cells, all cells undergo proliferation and cell death, and can secrete cytokines to regulate the proliferation of all cells. Drug-sensitive tumor cells can transit to drug-resistant tumor cells due to random gene mutations.

To formulate the model, we consider the numbers of normal, drug-sensitive and drug-resistant cells, which are represented by $x_1(t)$, $x_2(t)$ and $x_3(t)$, respectively. Dynamically, these three types of cells different from each other in their associated proliferation rates and removal rates.

Biologically, the self-renewal ability of a cell is determined by both microenvironmental conditions, *e.g.*, growth factor receptors and cell cycle checkpoints, such as fibroblast growth factors (FGFs) and the transforming growth factor beta (TGF-β) family [36–38]. The exact activation pathways that regulate the self-renewal of cells are poorly understood. However, a Hill type proliferation function can be derived based on simple but general assumptions on either positive or negative regulation growth factors [39, 40]. Let

$$c_i = \sum_{j=1}^{3} a_{ij} x_j, \qquad i = 1, 2, 3, \tag{2.1}$$

represent the overall effects of how cytokines secreted from all types of cells may regulate the self-renewal of type i cells, the competitions from cell type j to cell type i are given by the coefficients a_{ij} ($i, j = 1, 2, 3$). Thus, according to the Hill type function proposed in [39, 40], the proliferation rate for normal cells can be formulated as

$$\beta_1 \frac{\theta_1}{\theta_1 + c_1},$$

where β_1 represents the maximum proliferation rate of normal cells, and θ_1 is the 50% effective coefficient (EC50) that is associated with the effective concentration of cytokines. Here, we take the Hill coefficient to be 1 for simplicity. The proliferation rates of tumor cells are given similarly. However, tumor cells can escape the antigrowth signals due to the capability of self-sufficiency to growth signals and insensitivity to anti-growth signals [41], we thus introduce an additional nonzero

constant β_{i0} $(i = 2, 3)$ for the effects of self-sustained growth signals of tumor cells. Hence, the proliferation rates of drug-sensitive and drug-resistant cells are formulated as

$$\beta_2 \frac{\theta_2}{\theta_2 + c_2} + \beta_{20}, \quad \beta_3 \frac{\theta_3}{\theta_3 + c_3} + \beta_{30},$$

respectively.

The three types of cells undergo cell death with rates μ_i, respectively. Moreover, we assume that drug-sensitive cells can transit to drug-resistant cells with a rate η. These arguments give rise to the following model

$$\begin{cases} \dfrac{dx_1}{dt} &= \beta_1 \dfrac{\theta_1}{\theta_1 + c_1} x_1 - \mu_1 x_1, \\ \dfrac{dx_2}{dt} &= (\beta_2 \dfrac{\theta_2}{\theta_2 + c_2} + \beta_{20}) x_2 - \mu_2 x_2 - \eta x_2, \\ \dfrac{dx_3}{dt} &= (\beta_3 \dfrac{\theta_3}{\theta_3 + c_3} + \beta_{30}) x_3 - \mu_3 x_3 + \eta x_2. \end{cases} \tag{2.2}$$

Biologically, all parameters are non-negative, *i.e.*

$$\beta_i,\ \beta_{20},\ \beta_{30},\ \eta,\ a_{ij}\ (i \neq j) \geqslant 0,\ \theta_i,\ \mu_i,\ a_{ii} > 0, \quad i, j = 1, 2, 3. \tag{2.3}$$

Without loss of generality, we let

$$a_{ii} = 1\ (i = 1, 2, 3).$$

In the model (2.2), we apply Hill type functions to describe the proliferation rates of cells, which are derived based on the assumption of cell proliferation regulated by cytokines. Nevertheless, we note that in many studies, logistic growth or Gompertizian growth are often applied to model the dynamics of tumor growth [17–19, 22–24, 30]. These growth rate functions are consistent in describing the same property that cell growth rates decrease with the cell number, however are originated from difference biological assumptions. Biologically, Hill type growth rate is more proper to model tumor growth, by which the effects of cytokines are described explicitly.

In the current study, we would be always interested at the situation with positive cell numbers prior treatment. Thus, we have the following assumptions:

(H$_1$) The maximal proliferation rate β_1 is greater than the death rate μ_1 of normal cells, *i.e.*,

$$\xi_1 \triangleq \frac{\beta_1}{\mu_1} - 1 > 0. \tag{2.4}$$

(H$_2$) The maximal proliferation rate of drug-sensitive cells $(\beta_2 + \beta_{20})$ is larger than the total removal rate due to either cell death or transition $(\mu_2 + \eta)$, and the residual proliferation rate β_{20} should be smaller than the total removal rate to avoid infinity cell numbers (uncontrolled cell growth). These assumptions give

$$\xi_2 \triangleq \frac{\beta_2}{\mu_2 + \eta - \beta_{20}} - 1 > 0. \tag{2.5}$$

(H$_3$) The maximal proliferation rate of drug-resistant cells $(\beta_3 + \beta_{30})$ is larger than the cell death rate (μ_3), and the residual proliferation rate β_{30} should be smaller than the death rate to avoid infinity cell numbers (uncontrolled cell growth). These assumptions give

$$\xi_3 \triangleq \frac{\beta_3}{\mu_3 - \beta_{30}} - 1 > 0. \tag{2.6}$$

The assumptions (H_1)–(H_3) give biologically natural restrictions to the proliferation and death rates for the three types of cells.

3. Results

In this section, we first study the mathematical properties of the model (2.2), next consider the optimal strategy using PMP.

3.1. Invariant set of model solutions

Theorem 1. *Assume the conditions* (2.3)–(2.6)*, let*

$$\Omega = \{(x_1, x_2, x_3) \in \mathbb{R}^3 \mid 0 \leqslant x_1 \leqslant \xi_1\theta_1, 0 \leqslant x_2 \leqslant \xi_2\theta_2, 0 \leqslant x_3 \leqslant \frac{\beta_3\theta_3 + \eta\xi_2\theta_2}{\mu_3 - \beta_{30}}\}, \tag{3.1}$$

then Ω *is an invariant set of the model* (2.2)*, i.e., any solution of* (2.2) *with initial condition* $(x_{10}, x_{20}, x_{30}) \in \Omega$ *satisfies*

$$(x_1(t), x_2(t), x_3(t)) \in \Omega, \forall t \geqslant 0.$$

Proof. Let $(x_1(t), x_2(t), x_3(t))$ be the solution of the model (2.2) with initial condition $(x_{10}, x_{20}, x_{30}) \in \Omega$.

Firstly, it is easy to have

$$x_1(t) = x_{10}e^{\int_0^t (\frac{\beta_1\theta_1}{\theta_1 + x_1(s) + a_{12}x_2(s) + a_{13}x_3(s)} - \mu_1)ds} \geqslant 0, \quad \forall t \geqslant 0,$$

and

$$x_2(t) = x_{20}e^{\int_0^t (\frac{\beta_2\theta_2}{\theta_2 + a_{21}x_1(s) + x_2(s) + a_{23}x_3(s)} + \beta_{20} - \mu_2 - \eta)ds} \geqslant 0, \forall t \geqslant 0.$$

From the third equation of (2.2), we have

$$\frac{dx_3}{dt} \geqslant (\beta_3 \frac{\theta_3}{\theta_3 + a_{31}x_1(t) + a_{32}x_2(t) + x_3(t)} + \beta_{30})x_3 - \mu_3 x_3. \tag{3.2}$$

Multiplying both sides of (3.2) by $e^{-\int_0^t (\frac{\beta_3\theta_3}{\theta_3 + a_{31}x_1(s) + a_{32}x_2(s) + x_3(s)} + \beta_{30} - \mu_3)ds}$, we have

$$\left[\frac{dx_3}{dt} - \left((\beta_3 \frac{\theta_3}{\theta_3 + a_{31}x_1(t) + a_{32}x_2(t) + x_3(t)} + \beta_{30})x_3 - \mu_3 x_3\right)\right] e^{-\int_0^t (\frac{\beta_3\theta_3}{\theta_3 + a_{31}x_1(s) + a_{32}x_2(s) + x_3(s)} + \beta_{30} - \mu_3)ds} \geqslant 0,$$

which gives

$$\frac{d}{dt}\left[x_3(t)e^{-\int_0^t (\frac{\beta_3\theta_3}{\theta_3 + a_{31}x_1(s) + a_{32}x_2(s) + x_3(s)} + \beta_{30} - \mu_3)ds}\right] \geqslant 0. \tag{3.3}$$

Integrating (3.3) over $(0, t)$ with $x_3(0) = x_{30}$, we have

$$x_3(t)e^{-\int_0^t (\frac{\beta_3\theta_3}{\theta_3 + a_{31}x_1(s) + a_{32}x_2(s) + x_3(s)} + \beta_{30} - \mu_3)ds} - x_{30} \geqslant 0,$$

which gives

$$x_3(t) \geqslant x_{30}e^{\int_0^t (\frac{\beta_3\theta_3}{\theta_3 + a_{31}x_1(\tau) + a_{32}x_2(\tau) + x_3(\tau)} + \beta_{30} - \mu_3)d\tau} \geqslant 0.$$

Thus, any solution of (2.2) with nonnegative initial condition remains nonnegative over $t > 0$.

Next, we show that any nonnegative solution of (2.2) has finite upper bound. From the initial condition $x_1(0) = x_{10} \leqslant \xi_1\theta_1$ and

$$\begin{aligned}\frac{dx_1(t)}{dt}\Big|_{\{x_1=\xi_1\theta_1,x_2,x_3\geqslant 0\}} &= \beta_1\frac{\theta_1}{\theta_1+\xi_1\theta_1+a_{12}x_2+a_{13}x_3}\xi_1\theta_1-\mu_1\xi_1\theta_1\\ &\leqslant \beta_1\frac{\theta_1}{\theta_1+\xi_1\theta_1}\xi_1\theta_1-\mu_1\xi_1\theta_1\\ &= \beta_1\frac{\mu_1}{\beta_1}\xi_1\theta_1-\mu_1\xi_1\theta_1=0,\end{aligned}$$

we have $x_1(t) \leqslant \xi_1\theta_1, \forall t \geqslant 0$.

Similar calculations yield $x_2(t) \leqslant \xi_2\theta_2$ and $x_3(t) \leqslant \frac{\beta_3\theta_3+\eta\xi_2\theta_2}{\mu_3-\beta_{30}}, \forall t \geqslant 0$. This completes the proof.

3.2. Steady state solutions

3.2.1. Existence of steady state solutions

Now, we consider the steady state solutions of the model (2.2). Let (x_1^*, x_2^*, x_3^*) be the nonnegative steady state, we have

$$\begin{cases}\beta_1\dfrac{\theta_1}{\theta_1+c_1^*}x_1^*-\mu_1x_1^* &= 0,\\ (\beta_2\dfrac{\theta_2}{\theta_2+c_2^*}+\beta_{20})x_2^*-\mu_2x_2^*-\eta x_2^* &= 0,\\ (\beta_3\dfrac{\theta_3}{\theta_3+c_3^*}+\beta_{30})x_3^*-\mu_3x_3^*+\eta x_2^* &= 0,\end{cases} \tag{3.4}$$

where

$$c_1^* = x_1^*+a_{12}x_2^*+a_{13}x_3^*,\quad c_2^* = a_{21}x_1^*+x_2^*+a_{23}x_3^*,\quad c_3^* = a_{31}x_1^*+a_{32}x_2^*+x_3^*.$$

We are only interested at the steady states that the cell numbers are nonnegative, which can be divided into one of the 8 possible types $(+/0, +/0, +/0)$, here '+' means a positive number, and '0' means zero. It is easy to see that, there always exists a zero steady sate $E_0 = (0, 0, 0)$, however this state represents the state of death and is biologically not interested. Since $\eta > 0$, $x_3^* = 0$ always implies $x_2^* = 0$, there is no steady state of form $(0, +, 0)$ or $(+, +, 0)$. Thus, there are 6 possible steady states (here $x_i^* > 0$)

$$\begin{gathered}E_0 = (0,0,0),\ E_1 = (x_1^*,0,0),\ E_3 = (0,0,x_3^*),\\ E_{13} = (x_1^*,0,x_3^*),\ E_{23} = (0,x_2^*,x_3^*),\ E_{123} = (x_1^*,x_2^*,x_3^*).\end{gathered} \tag{3.5}$$

The theorem below gives the existence of nonnegative steady states.

Theorem 2. *Consider the model* (2.2)*, and assume that all parameters satisfy* (2.3)*.*

(1) *There always exists the zero steady state* $E_0 = (0, 0, 0)$.
(2) *If* (2.4) *holds,* (2.2) *has tumor-free equilibrium* $E_1 = (\xi_1\theta_1, 0, 0)$.
(3) *If* (2.6) *holds,* (2.2) *has normal-free equilibrium* $E_3 = (0, 0, \xi_3\theta_3)$.

(4) *If both* (2.4) *and* (2.6) *hold, let*

$$s_2 = 1 - a_{13}a_{31},\ \xi_4 = \xi_1\theta_1 - a_{13}\xi_3\theta_3,\ \xi_5 = \xi_3\theta_3 - a_{31}\xi_1\theta_1, \tag{3.6}$$

(2.2) *has one steady state of form* $E_{13} = (\frac{\xi_4}{s_2}, 0, \frac{\xi_5}{s_2})$ *only when* s_2, ξ_4 *and* ξ_5 *are non-zero and have the same sign.*

(5) *If both* (2.5) *and* (2.6) *hold, then*

(i) *if* $a_{23} > \dfrac{\xi_2\theta_2}{\xi_3\theta_3}$, *let*

$$\begin{aligned} p_1 &= a_{32} + \frac{\theta_3}{\xi_2\theta_2}, \\ q_1 &= 1 + a_{32}\frac{\beta_{30} - \mu_3}{\eta} + \frac{\theta_3}{\xi_2\theta_2}(a_{23} + \frac{\beta_3 + \beta_{30} - \mu_3}{\eta}), \\ r_1 &= \frac{a_{23}\theta_3}{\xi_2\theta_2}\frac{\beta_3 + \beta_{30} - \mu_3}{\eta} - \frac{\mu_3 - \beta_{30}}{\eta}, \end{aligned} \tag{3.7}$$

if

$$0 < -\frac{q_1}{2p_1} < \frac{\mu_3 - \beta_{30}}{\eta}, \quad q_1^2 - 4p_1r_1 > 0\ (or\ = 0), \tag{3.8}$$

(2.2) *has two (or one) steady state of* E_{23}*-type; otherwise,* (2.2) *has no steady state of* E_{23}*-type.*

(ii) *if* $a_{23} < \dfrac{\xi_2\theta_2}{\xi_3\theta_3}$, (2.2) *has one and only one steady state of* E_{23}*-type.*

(6) *If* (2.4)–(2.6) *hold,* (2.2) *has at most two steady states of form* $E_{123} = (x_1^*, x_2^*, x_3^*)$. *Moreover, let*

$$\begin{aligned} p_2 &= -(s_3 + a_{31}(a_{12}a_{23} - a_{13}) + a_{32}(a_{13}a_{21} - a_{23}))(s_3(\mu_3 - \beta_{30}) - \eta(a_{13}a_{21} - a_{23})), \\ q_2 &= s_3^2\theta_3(\beta_3 + \beta_{30} - \mu_3) + s_3\Big(\eta\theta_3(a_{13}a_{21} - a_{23}) + \xi_1\theta_1((a_{21}a_{32} - a_{31})(\mu_3 - \beta_{30}) - \eta a_{21}) \\ &\quad + \xi_2\theta_2((a_{12}a_{31} - a_{32})(\mu_3 - \beta_{30}) + \eta)\Big) \\ &\quad - \eta\xi_1\theta_1((a_{21}a_{32} - a_{31})(2a_{13}a_{21} - a_{23}) + a_{23}a_{21}(a_{12}a_{31} - a_{32})) \\ &\quad - \eta\xi_2\theta_2((a_{12}a_{31} - a_{32})(a_{13}a_{21} - 2a_{23}) - a_{13}(a_{21}a_{32} - a_{31})), \\ r_2 &= -\eta(\xi_1\theta_1a_{21} - \xi_2\theta_2)(s_3\theta_3 - \xi_1\theta_1(a_{21}a_{32} - a_{31}) - \xi_2\theta_2(a_{12}a_{31} - a_{32})), \end{aligned} \tag{3.9}$$

where $s_3 = 1 - a_{21}a_{12} \neq 0$, *the* E_{123}*-type steady states are determined by the solutions* $x_3 = x_3^*$ *of the equation*

$$p_2{x_3}^2 + q_2x_3 + r_2 = 0, \tag{3.10}$$

and the solution x_3^* *satisfy: if* $s_3 > 0$,

$$\frac{1}{a_{21}}(\xi_2\theta_2 - a_{23}x_3^*) > (\xi_1\theta_1 - a_{13}x_3^*) > a_{12}(\xi_2\theta_2 - a_{23}x_3^*), \tag{3.11}$$

and if $s_3 < 0$,

$$a_{12}(\xi_2\theta_2 - a_{23}x_3^*) > (\xi_1\theta_1 - a_{13}x_3^*) > \frac{1}{a_{21}}(\xi_2\theta_2 - a_{23}x_3^*) > 0. \tag{3.12}$$

In this case, x_1^* and x_2^* are given by

$$x_1^* = \frac{1}{s_3}((\xi_1\theta_1 - a_{13}x_3^*) - a_{12}(\xi_2\theta_2 - a_{23}x_3^*)), \tag{3.13}$$

$$x_2^* = \frac{1}{s_3}((\xi_2\theta_2 - a_{23}x_3^*) - a_{21}(\xi_1\theta_1 - a_{13}x_3^*)). \tag{3.14}$$

Proof. (1). It is trivial to see that model (2.2) always has the zero steady state E_0.

(2). Let $x_2^* = x_3^* = 0$ and $x_1^* \neq 0$, from the first equation of (2.2), x_1^* satisfies

$$\beta_1 \frac{\theta_1}{\theta_1 + x_1^*} x_1^* - \mu_1 x_1^* = 0, \tag{3.15}$$

which gives

$$\beta_1 \frac{\theta_1}{\theta_1 + x_1^*} - \mu_1 = 0. \tag{3.16}$$

Hence, condition (2.4) implies

$$x_1^* = (\frac{\beta_1}{\mu_1} - 1)\theta_1 = \xi_1\theta_1 > 0.$$

(3). Let $x_1^* = x_2^* = 0$ and $x_3^* \neq 0$. From the third equation of (3.4), we have

$$(\beta_3 \frac{\theta_3}{\theta_3 + x_3^*} + \beta_{30})x_3^* - \mu_3 x_3^* = 0, \tag{3.17}$$

which gives

$$\beta_3 \frac{\theta_3}{\theta_3 + x_3^*} + \beta_{30} - \mu_3 = 0. \tag{3.18}$$

Thus, condition (2.6) implies

$$x_3^* = (\frac{\beta_3}{\mu_3 - \beta_{30}} - 1)\theta_3 = \xi_3\theta_3 > 0.$$

(4) Let $x_2^* = 0$, the first and the third equation of (3.4) become

$$\begin{cases} \beta_1 \dfrac{\theta_1}{\theta_1 + x_1^* + a_{13}x_3^*} x_1^* - \mu_1 x_1^* = 0, \\ (\beta_3 \dfrac{\theta_3}{\theta_3 + a_{31}x_1^* + x_3^*} + \beta_{30})x_3^* - \mu_3 x_3^* = 0. \end{cases} \tag{3.19}$$

Given $x_1^*, x_3^* \neq 0$, (3.19) can be rewritten as

$$\begin{cases} \beta_1 \dfrac{\theta_1}{\theta_1 + x_1^* + a_{13}x_3^*} - \mu_1 = 0, \\ \beta_3 \dfrac{\theta_3}{\theta_3 + a_{31}x_1^* + x_3^*} + \beta_{30} - \mu_3 = 0, \end{cases} \tag{3.20}$$

which yields

$$\begin{cases} x_1^* + a_{13}x_3^* &= \xi_1\theta_1, \\ a_{31}x_1^* + x_3^* &= \xi_3\theta_3. \end{cases} \tag{3.21}$$

From (3.21), we obtain

$$x_1^* = \frac{\xi_4}{s_2}, \quad x_3^* = \frac{\xi_5}{s_2}$$

when s_2, ξ_4 and ξ_5 are given by (3.6). Thus, (2.2) has a steady state of form E_{13} only when s_2, ξ_4 and ξ_5 are non-zero and have the same sign.

(5). To consider the steady state of form E_{23}, let $x_1^* = 0$ in (3.4), we obtain

$$\begin{cases} (\beta_2\frac{\theta_2}{\theta_2 + x_2^* + a_{23}x_3^*} + \beta_{20})x_2^* - \mu_2 x_2^* - \eta x_2^* &= 0, \\ (\beta_3\frac{\theta_3}{\theta_3 + a_{32}x_2^* + x_3^*} + \beta_{30})x_3^* - \mu_3 x_3^* + \eta x_2^* &= 0. \end{cases} \tag{3.22}$$

When $x_2^*, x_3^* \neq 0$, (3.22) can be rewritten as

$$\begin{cases} \beta_2\frac{\theta_2}{\theta_2 + x_2^* + a_{23}x_3^*} &= \mu_2 + \eta - \beta_{20}, \\ \beta_3\frac{\theta_3}{\theta_3 + a_{32}x_2^* + x_3^*} &= \mu_3 - \eta\frac{x_2^*}{x_3^*} - \beta_{30}. \end{cases} \tag{3.23}$$

Thus, we have

$$\begin{cases} x_2^* + a_{23}x_3^* &= \xi_2\theta_2, \\ a_{32}x_2^* + x_3^* &= (\frac{\beta_3}{\mu_3 - \eta x_2^*/x_3^* - \beta_{30}} - 1)\theta_3. \end{cases} \tag{3.24}$$

Dividing both sides of (3.24) by x_3^*, we have

$$\begin{cases} x_2^*/x_3^* + a_{23} &= \xi_2\theta_2/x_3^*, \\ a_{32}x_2^*/x_3^* + 1 &= (\frac{\beta_3}{\mu_3 - \eta x_2^*/x_3^* - \beta_{30}} - 1)\theta_3/x_3^*. \end{cases} \tag{3.25}$$

Denote $y^* = \frac{x_2^*}{x_3^*}$ and $z^* = \frac{1}{x_3^*}$, then

$$0 < y^* < \frac{\mu_3 - \beta_{30}}{\eta}, \quad z^* > 0,$$

and (3.25) becomes

$$\begin{cases} y^* + a_{23} &= \xi_2\theta_2 z^*, \\ a_{32}y^* + 1 &= (\frac{\beta_3}{\mu_3 - \eta y^* - \beta_{30}} - 1)\theta_3 z^*. \end{cases} \tag{3.26}$$

The first equation of (3.26) implies

$$z^* = \frac{y^* + a_{23}}{\xi_2\theta_2}. \tag{3.27}$$

The second equation of (3.26) implies

$$z^* = \frac{(a_{32}y^* + 1)(\mu_3 - \eta y^* - \beta_{30})}{\theta_3(\beta_3 - \mu_3 + \eta y^* + \beta_{30})}. \tag{3.28}$$

Hence, (3.27) and (3.28) together give the equation for $y = y^*$,

$$\frac{y + a_{23}}{\xi_2\theta_2} = \frac{(a_{32}y + 1)(\mu_3 - \eta y - \beta_{30})}{\theta_3(\beta_3 - \mu_3 + \eta y + \beta_{30})},$$

which implies

$$f(y) \triangleq p_1y^2 + q_1y + r_1 = 0, \tag{3.29}$$

where p_1, q_1, r_1 are given by (3.7). Thus, to get the positive solution of (3.26), we only need to solve the equation (3.29) for the solution $0 < y^* < \frac{\mu_3-\beta_{30}}{\eta}$.

When (3.29) has a solution $y^* \in (0, \frac{\mu_3 - \beta_{30}}{\eta})$, we have $z^* > 0$ from (3.27), and the nonnegative steady state $E_{23} = (0, x_2^*, x_3^*)$ is given by $x_2^* = \frac{y^*}{z^*}$ and $x_3^* = \frac{1}{z^*}$. Now, we identify the conditions to have such a solution based on the competition coefficient a_{23}.

(i) If $a_{23} > \frac{\xi_2\theta_2}{\xi_3\theta_3}$, we have $p_1 > 0$, and

$$\begin{aligned} f(0) &= \frac{a_{23}\theta_3}{\xi_2\theta_2}\frac{\beta_3 + \beta_{30} - \mu_3}{\eta} - \frac{\mu_3 - \beta_{30}}{\eta} \\ &> \frac{1}{\xi_3}\frac{\beta_3 + \beta_{30} - \mu_3}{\eta} - \frac{\mu_3 - \beta_{30}}{\eta} \\ &= \frac{1}{\xi_3}\frac{\beta_3}{\eta} - (\frac{1}{\xi_3} + 1)\frac{\mu_3 - \beta_{30}}{\eta} \\ &= \frac{1}{\xi_3}\frac{\beta_3}{\eta} - \frac{1}{\xi_3}\frac{\beta_3}{\mu_3 - \beta_{30}}\frac{\mu_3 - \beta_{30}}{\eta} \\ &= 0. \end{aligned} \tag{3.30}$$

Moreover,

$$f(\frac{\mu_3 - \beta_{30}}{\eta}) = \frac{\beta_3\theta_3}{\eta\xi_2\theta_2}(a_{23} + \frac{\mu_3 - \beta_{30}}{\eta}) > 0.$$

Hence, if

$$0 < -\frac{q_1}{2p_1} < \frac{\mu_3 - \beta_{30}}{\eta}, \quad q_1^2 - 4p_1r_1 > 0 \text{ (or } = 0),$$

(3.29) has two (or one) positive solutions in the interval $(0, \frac{\mu_3-\beta_{30}}{\eta})$, *i.e.*, (2.2) has two (or one) steady states of E_{23}-type; otherwise, (2.2) has no steady state of E_{23}-type.

(ii) If $a_{23} < \dfrac{\xi_2\theta_2}{\xi_3\theta_3}$, similar to the above argument of (3.30), we have

$$f(0) < \frac{1}{\xi_3}\frac{\beta_3+\beta_{30}-\mu_3}{\eta} - \frac{\mu_3-\beta_{30}}{\eta} = 0.$$

Thus, since,

$$f(\frac{\mu_3-\beta_{30}}{\eta}) > 0,$$

the quadratic function $f(y)$ has one and only one root in $(0, \dfrac{\mu_3-\beta_{30}}{\eta})$, *i.e.*, (2.2) has one and only one steady state of E_{23}-type.

(6). To consider the positive steady sate of form $E_{123} = (x_1^*, x_2^*, x_3^*)$, we need to find the positive solution of

$$\begin{cases} \beta_1\dfrac{\theta_1}{\theta_1+x_1^*+a_{12}x_2^*+a_{13}x_3^*} - \mu_1 &= 0, \\ \beta_2\dfrac{\theta_2}{\theta_2+a_{21}x_1^*+x_2^*+a_{23}x_3^*} + \beta_{20} - \mu_2 - \eta &= 0, \\ (\beta_3\dfrac{\theta_3}{\theta_3+a_{31}x_1^*+a_{32}x_2^*+x_3^*} + \beta_{30})x_3^* - \mu_3x_3^* + \eta x_2^* &= 0. \end{cases} \tag{3.31}$$

From the first and the second equations of (3.31), we have

$$\begin{cases} x_1^* + a_{12}x_2^* &= \xi_1\theta_1 - a_{13}x_3^*, \\ a_{21}x_1^* + x_2^* &= \xi_2\theta_2 - a_{23}x_3^*, \end{cases} \tag{3.32}$$

which gives

$$\begin{cases} x_1^* &= \dfrac{1}{s_3}((\xi_1\theta_1 - a_{13}x_3^*) - a_{12}(\xi_2\theta_2 - a_{23}x_3^*)), \\ x_2^* &= \dfrac{1}{s_3}((\xi_2\theta_2 - a_{23}x_3^*) - a_{21}(\xi_1\theta_1 - a_{13}x_3^*)), \end{cases} \tag{3.33}$$

where $s_3 = 1 - a_{21}a_{12} \neq 0$.

Substituting (3.33) into the third equation of (3.31), x_3^* satisfies the quadratic equation

$$p_2{x_3^*}^2 + q_2x_3^* + r_2 = 0, \tag{3.34}$$

where p_2, q_2 and r_2 are given by (3.9). Moreover, from (3.32) and (3.33), if $s_3 > 0$, x_3^* should satisfy

$$\frac{1}{a_{21}}(\xi_2\theta_2 - a_{23}x_3^*) > (\xi_1\theta_1 - a_{13}x_3^*) > a_{12}(\xi_2\theta_2 - a_{23}x_3^*) > 0; \tag{3.35}$$

and if $s_3 < 0$, x_3^* satisfies

$$a_{12}(\xi_2\theta_2 - a_{23}x_3^*) > (\xi_1\theta_1 - a_{13}x_3^*) > \frac{1}{a_{21}}(\xi_2\theta_2 - a_{23}x_3^*) > 0. \tag{3.36}$$

Thus, (2.2) has at most two steady states of form E_{123}, which are determined by the solutions of (3.34) and (3.33) with x_3^* satisfies (3.35) when $s_3 > 0$, or (3.36) when $s_3 < 0$.

Theorem 2 establishes the conditions for the existence of nonnegative steady states of different types. Biologically, the conditions (2.4)–(2.6) are satisfied by most tissue cells, and hence the steady states of types E_0, E_1 and E_3 always exist. Moreover, under the extreme condition when the competition coefficients $a_{ij} = 0$ for any $i \neq j$, it is easy to have the existence of the steady states of types E_{13} and E_{23} from (4) and (5), and from (6),

$$p_2 = -(\mu_3 - \beta_{30}) < 0,\ r_2 = \eta\theta_2\theta_3\xi_2 > 0, s_3 = 1 > 0,$$

which yield the existence of a steady state of type E_{123}. Thus, from the continuous dependence, the proposed model (2.2) have steady states of all types in (3.5) when the competition coefficients $a_{ij} > 0$ ($i \neq j$) are small enough.

3.2.2. Stability of steady states

Now, we study the stability of the steady state $E^* = (x_1^*, x_2^*, x_3^*)$. Let $x = x_1 - x_1^*$, $y = x_2 - x_2^*$ and $z = x_3 - x_3^*$, and linearize the model (2.2) at E^*, we have the linearization equation

$$\begin{cases} \dfrac{dx}{dt} &= A_1x + A_2y + A_3z, \\ \dfrac{dy}{dt} &= B_1x + B_2y + B_3z, \\ \dfrac{dz}{dt} &= C_1x + C_2y + C_3z, \end{cases} \tag{3.37}$$

where

$$A_1 = \frac{\theta_1\beta_1}{\theta_1 + c_1^*} - \mu_1 - \alpha_1,\ A_2 = -a_{12}\alpha_1,\ A_3 = -a_{13}\alpha_1,$$

$$B_1 = -a_{21}\alpha_2,\ B_2 = \frac{\theta_2\beta_2}{\theta_2 + c_2^*} + \beta_{20} - \mu_2 - \eta - \alpha_2,\ B_3 = -a_{23}\alpha_2,$$

$$C_1 = -a_{31}\alpha_3,\ C_2 = -a_{32}\alpha_3 + \eta,\ C_3 = \frac{\theta_3\beta_3}{\theta_3 + c_3^*} - \alpha_3 - \mu_3 + \beta_{30},$$

$$\alpha_1 = \frac{\beta_1\theta_1x_1^*}{(\theta_1 + c_1^*)^2},\ \alpha_2 = \frac{\beta_2\theta_2x_2^*}{(\theta_2 + c_2^*)^2},\ \alpha_3 = \frac{\beta_3\theta_3x_3^*}{(\theta_3 + c_3^*)^2}.$$

The characteristic equation of (3.37) is written as

$$\lambda^3 + a\lambda^2 + b\lambda + c = 0. \tag{3.38}$$

where

$$\begin{aligned} &a = -(A_1 + B_2 + C_3),\ b = B_2C_3 + A_1B_2 + A_1C_3 - B_3C_2 - A_2B_1 - A_3C_1, \\ &c = -A_1B_2C_3 + A_1B_3C_2 + A_2B_1C_3 - A_3B_1C_2 - A_2B_3C_1 + A_3B_2C_1. \end{aligned} \tag{3.39}$$

Based on the characteristic Eq (3.39), the condition for asymptotical stability of steady states are given by the Theorem below.

Theorem 3. *Consider the model*(2.2)*, and assume that all parameters satisfy* (2.3) *and the conditions for the existence of steady states listed in Theorem 2, we have the following results.*

(1) *The zero steady state* $E_0 = (0, 0, 0)$ *is asymptotically stable if and only if none of the conditions* (2.4)–(2.6) *holds, i.e.,*

$$\beta_1 - \mu_1 < 0, \quad \beta_2 + \beta_{20} - \mu_2 < \eta, \quad \beta_3 + \beta_{30} - \mu_3 < 0. \tag{3.40}$$

Furthermore, if

$$\beta_1 - \mu_1 < 0, \quad \beta_2 + \beta_{20} - \mu_2 < 0, \quad \beta_3 + \beta_{30} - \mu_3 < 0, \tag{3.41}$$

E_0 *is globally stable for any solutions in* Ω.

(2) *If* (2.4) *holds, the steady state* $E_1 = (x_1^*, 0, 0)$ *is asymptotically stable if and only if*

$$\frac{\xi_2\theta_2}{\xi_1\theta_1} < a_{21}, \quad \frac{\xi_3\theta_3}{\xi_1\theta_1} < a_{31}. \tag{3.42}$$

(3) *If* (2.6) *holds, the steady state* $E_3 = (0, 0, x_3^*)$ *is asymptotically stable if and only if*

$$\frac{\xi_1\theta_1}{\xi_3\theta_3} < a_{13}, \quad \frac{\xi_2\theta_2}{\xi_3\theta_3} < a_{23}. \tag{3.43}$$

(4) *If* (2.4) *and* (2.6) *hold, the steady state* $E_{13} = (x_1^*, 0, x_3^*)$ *is asymptotically stable if and only if*

$$1 - a_{13}a_{31} > 0, \quad \text{and} \quad \xi_2\theta_2 < a_{21}x_1^* + a_{23}x_3^*. \tag{3.44}$$

(5) *If* (2.5) *and* (2.6) *hold, the steady state* $E_{23} = (0, x_2^*, x_3^*)$ *is asymptotically stable if and only if*

$$\xi_1\theta_1 < a_{12}x_2^* + a_{13}x_3^*, \quad (1 - a_{23}a_{32}) + \frac{\eta}{\beta_3\theta_3 x_3^*}\left(\frac{x_2^*}{x_3^*} + a_{23}\right)(\theta_3 + a_{32}x_2^* + x_3^*)^2 > 0. \tag{3.45}$$

(6) *If* (2.4)–(2.6) *hold, the steady state* $E_{123} = (x_1^*, x_2^*, x_3^*)$ *is asymptotically stable if and only if*

$$a > 0, \quad ab - c > 0, \quad c > 0, \tag{3.46}$$

where a, b, c *are defined by* (3.39). *Particularly, if the following conditions are satisfied*

$$\begin{aligned} &\xi_1, \xi_2, \xi_3 > 0, \\ &1 - a_{23}a_{32} - a_{12}a_{21} - a_{13}a_{31} + a_{13}a_{21}a_{32} + a_{12}a_{23}a_{31} > 0, \\ &2 - a_{13}a_{21}a_{32} - a_{12}a_{23}a_{31} \geqslant 0, \\ &1 - a_{23}a_{32} \geqslant 0,\ 1 - a_{12}a_{21} > 0,\ 1 - a_{13}a_{31} \geqslant 0,\ a_{23} - a_{13}a_{21} \geqslant 0, \end{aligned} \tag{3.47}$$

E_{123} *is asymptotically stable.*

Proof. (1) For the steady state E_0, the coefficient matrix of the linearized Eq (3.37) is

$$J_{E_0} = \begin{pmatrix} \beta_1 - \mu_1 & 0 & 0 \\ 0 & \beta_2 + \beta_{20} - \mu_2 - \eta & 0 \\ 0 & \eta & \beta_3 + \beta_{30} - \mu_3 \end{pmatrix}. \tag{3.48}$$

It is straight forward to obtain the corresponding eigenvalues

$$\lambda_1 = \beta_1 - \mu_1,\ \lambda_2 = \beta_2 + \beta_{20} - \mu_2 - \eta,\ \lambda_3 = \beta_3 + \beta_{30} - \mu_3.$$

Thus, E_0 is asymptotically stable if and only if $\lambda_1, \lambda_2, \lambda_3 < 0$, *i.e.*, none of the conditions (2.4)–(2.6) holds.

Next, to show the global stability of E_0, we construct a Lyapunov function $V(x_1, x_2, x_3)$ as

$$V(x_1, x_2, x_3) = \frac{1}{2}(x_1^2 + (x_2 + x_3)^2). \tag{3.49}$$

It is easy to see that $V(x_1, x_2, x_3)$ is positive definite, and the derivative of $V(x_1(t), x_2(t), x_3(t))$ along any solution of (2.2) is given by

$$\begin{aligned}\left.\frac{dV(x_1(t), x_2(t), x_3(t))}{dt}\right|_{(2.2)} &= (x_1\dot{x}_1 + (x_2 + x_3)(\dot{x}_2 + \dot{x}_3))|_{(2.2)} \\ &= (\beta_1\frac{\theta_1}{\theta_1 + c_1} - \mu_1)x_1^2 \\ &\quad + (x_2 + x_3)\left((\beta_2\frac{\theta_2}{\theta_2 + c_2} + \beta_{20} - \mu_2)x_2 + (\beta_3\frac{\theta_3}{\theta_3 + c_3} + \beta_{30} - \mu_3)x_3\right).\end{aligned} \tag{3.50}$$

From Theorem 1 and the proof therein, any solution of (2.2) with initial condition $(x_{10}, x_{20}, x_{30}) \in \Omega$ remains in Ω for all $t > 0$, *i.e.*, $x_1(t), x_2(t), x_3(t) \geqslant 0$. Hence, when (3.41) is satisfied, the derivative (3.50) along any solution in Ω is negative definite. According to Theorem 1.1 in chapter X.1 of [36], E_0 is globally stable for any solutions in Ω.

(2) For the steady state $E_1 = (x_1^*, 0, 0)$, the coefficient matrix of Eq (3.37) is

$$J_{E_1} = \begin{pmatrix} -\frac{\mu_1(\beta_1 - \mu_1)}{\beta_1} & -a_{12}\frac{\beta_1\theta_1 x_1^*}{(\theta_1 + x_1^*)^2} & -a_{13}\frac{\beta_1\theta_1 x_1^*}{(\theta_1 + x_1^*)^2} \\ 0 & \frac{\beta_2\theta_2}{\theta_2 + a_{21}\xi_1\theta_1} + \beta_{20} - \mu_2 - \eta & 0 \\ 0 & \eta & \frac{\beta_3\theta_3}{\theta_3 + a_{31}\xi_1\theta_1} + \beta_{30} - \mu_3 \end{pmatrix}. \tag{3.51}$$

It is easy to have the eigenvalues

$$\begin{aligned}\lambda_1 &= -\frac{\mu_1(\beta_1 - \mu_1)}{\beta_1} \\ \lambda_2 &= \frac{\beta_2\theta_2}{\theta_2 + a_{21}\xi_1\theta_1} + \beta_{20} - \mu_2 - \eta, \\ \lambda_3 &= \frac{\beta_3\theta_3}{\theta_3 + a_{31}\xi_1\theta_1} + \beta_{30} - \mu_3.\end{aligned}$$

When (2.4) holds, we have $\xi_1 > 0$, and $\lambda_1 < 0$. Moreover, we have

$$\begin{aligned}\lambda_2 < 0 &\iff \frac{\beta_2\theta_2}{\theta_2 + a_{21}\xi_1\theta_1} + \beta_{20} - \mu_2 - \eta < 0 \\ &\iff \beta_2\theta_2 < (\mu_2 + \eta - \beta_{20})(\theta_2 + a_{21}\xi_1\theta_1) \text{ and } (\mu_2 + \eta - \beta_{20}) > 0 \\ &\iff \frac{\beta_2\theta_2}{\mu_2 + \eta - \beta_{20}} < \theta_2 + a_{21}\xi_1\theta_1 \\ &\iff \frac{\xi_2\theta_2}{\xi_1\theta_1} < a_{21}.\end{aligned}$$

and

$$\begin{aligned}\lambda_3 < 0 \quad &\Longleftrightarrow \quad \frac{\beta_3\theta_3}{\theta_3 + a_{31}\xi_1\theta_1} + \beta_{30} - \mu_3 < 0\\ &\Longleftrightarrow \quad \beta_3\theta_3 < (\mu_3 - \beta_{30})(\theta_3 + a_{31}\xi_1\theta_1) \text{ and } (\mu_3 - \beta_{30}) > 0\\ &\Longleftrightarrow \quad \frac{\beta_3\theta_3}{\mu_3 - \beta_{30}} < \theta_3 + a_{31}\xi_1\theta_1\\ &\Longleftrightarrow \quad \frac{\xi_3\theta_3}{\xi_1\theta_1} < a_{31}.\end{aligned}$$

Thus, E_1 is asymptotically stable if and only if $\lambda_2 < 0$ and $\lambda_3 < 0$, *i.e.*, $\frac{\xi_2\theta_2}{\xi_1\theta_1} < a_{21}$ and $\frac{\xi_3\theta_3}{\xi_1\theta_1} < a_{31}$.

(3) For the steady state $E_3 = (0, 0, x_3^*)$, the coefficient matrix of (3.37) is given by

$$J_{E_1} = \begin{pmatrix} \frac{\beta_1\theta_1}{\theta_1 + a_{13}x_3^*} - \mu_1 & 0 & 0\\ 0 & \frac{\beta_2\theta_2}{\theta_2 + a_{23}x_3^*} + \beta_{20} - \mu_2 - \eta & 0\\ -a_{31}\frac{\beta_3\theta_3 x_3^*}{(\theta_3 + x_3^*)^2} & -a_{32}\frac{\beta_3\theta_3 x_3^*}{(\theta_3 + x_3^*)^2} + \eta & -\frac{(\mu_3 - \beta_{30})(\beta_3 + \beta_{30} - \mu_3)}{\beta_3} \end{pmatrix}. \tag{3.52}$$

This, it is straight forward to have the eigenvalues λ_1, λ_2, and λ_3 as:

$$\begin{aligned}\lambda_1 &= \frac{\beta_1\theta_1}{\theta_1 + a_{13}x_3^*} - \mu_1,\\ \lambda_2 &= \frac{\beta_2\theta_2}{\theta_2 + a_{23}x_3^*} + \beta_{20} - \mu_2 - \eta,\\ \lambda_3 &= -\frac{(\mu_3 - \beta_{30})(\beta_3 + \beta_{30} - \mu_3)}{\beta_3}.\end{aligned}$$

From the condition (2.6), we have $\xi_3 > 0$, and hence $\lambda_3 < 0$. Moreover, note $x_3^* = \xi_3\theta_3$, similar to the argument in (2), we have

$$\lambda_1 = \frac{\beta_1\theta_1}{\theta_1 + a_{13}\xi_3\theta_3} - \mu_1 < 0 \iff \frac{\beta_1\theta_1}{\mu_1} < \theta_1 + a_{13}\xi_3\theta_3 \iff \frac{\xi_1\theta_1}{\xi_3\theta_3} < a_{13},$$

and

$$\lambda_2 = \frac{\beta_2\theta_2}{\theta_2 + a_{23}\xi_3\theta_3} + \beta_{20} - \mu_2 - \eta < 0 \iff \frac{\beta_2\theta_2}{\mu_2 + \eta - \beta_{20}} < \theta_2 + a_{23}\xi_3\theta_3 \iff \frac{\xi_2\theta_2}{\xi_3\theta_3} < a_{23}.$$

Hence, E_3 is asymptotically stable if and only if $\lambda_1 < 0$ and $\lambda_2 < 0$, *i.e.*, $\frac{\xi_1\theta_1}{\xi_3\theta_3} < a_{13}$ and $\frac{\xi_2\theta_2}{\xi_3\theta_3} < a_{23}$.

(4) For the steady state $E_{13} = (x_1^*, 0, x_3^*)$, the coefficient matrix of (3.37) is given by

$$J_{E_{13}} = \begin{pmatrix} -\alpha_4 & -a_{12}\alpha_4 & -a_{13}\alpha_4\\ 0 & \frac{\beta_2\theta_2}{\theta_2 + a_{21}x_1^* + a_{23}x_3^*} + \beta_{20} - \mu_2 - \eta & 0\\ -a_{31}\alpha_5 & \eta - a_{32}\alpha_5 & -\alpha_5 \end{pmatrix}, \tag{3.53}$$

where

$$\alpha_4 = \frac{\beta_1\theta_1 x_1^*}{(\theta_1 + x_1^* + a_{13}x_3^*)^2},\ \alpha_5 = \frac{\beta_3\theta_3 x_3^*}{(\theta_1 + a_{31}x_1^* + x_3^*)^2}.$$

The eigenvalues λ_1, λ_2 and λ_3 of $J_{E_{13}}$ satisfy

$$\lambda_1 + \lambda_3 = -(\alpha_4 + \alpha_5),\ \lambda_1\lambda_3 = (1 - a_{13}a_{31})\alpha_4\alpha_5$$

and

$$\lambda_2 = \frac{\beta_2\theta_2}{\theta_2 + a_{21}x_1^* + a_{23}x_3^*} + \beta_{20} - \mu_2 - \eta.$$

Since $\alpha_4 > 0, \alpha_5 > 0$, we have $\lambda_1 < 0, \lambda_3 < 0$ if and only if $1 - a_{13}a_{31} > 0$. Moreover, similar to the previous argument,

$$\lambda_2 < 0 \iff \beta_2\theta_2 < (\mu_2 + \eta - \beta_{30})(\theta_2 + a_{21}x_1^* + a_{23}x_3^*) \iff \xi_2\theta_2 < a_{21}x_1^* + a_{23}x_3^*.$$

Thus, E_{13} is asymptotically stable if and only if (3.44) is satisfied.

(5) For the steady state $E_{23} = (0, x_2^*, x_3^*)$, the coefficient matrix of (3.37) is given by

$$J_{E_{23}} = \begin{pmatrix} \frac{\beta_1\theta_1}{\theta_1 + a_{12}x_2^* + a_{13}x_3^*} - \mu_1 & 0 & 0 \\ -a_{21}\alpha_6 & -\alpha_6 & -a_{23}\alpha_6 \\ -a_{31}\alpha_7 & \eta - a_{32}\alpha_7 & -\frac{\eta x_2^*}{x_3^*} - \alpha_7 \end{pmatrix}, \tag{3.54}$$

where

$$\alpha_6 = \frac{\beta_2\theta_2 x_2^*}{(\theta_2 + x_2^* + a_{23}x_3^*)^2},\ \alpha_7 = \frac{\beta_3\theta_3 x_3^*}{(\theta_3 + a_{32}x_2^* + x_3^*)^2}.$$

The eigenvalues λ_1, λ_2 and λ_3 of $J_{E_{23}}$ satisfy

$$\lambda_1 = \frac{\beta_1\theta_1}{\theta_1 + a_{12}x_2^* + a_{13}x_3^*} - \mu_1,$$

and

$$\lambda_2 + \lambda_3 = -(\alpha_6 + \frac{\eta x_2^*}{x_3^*} + \alpha_7), \quad \text{and} \quad \lambda_2\lambda_3 = \alpha_6((1 - a_{23}a_{32})\alpha_7 + \eta(\frac{x_2^*}{x_3^*} + a_{23})).$$

Similar to the previous argument,

$$\lambda_1 < 0 \iff \frac{\beta_1\theta_1}{\theta_1 + a_{12}x_2^* + a_{13}x_3^*} < \mu_1 \iff \xi_1\theta_1 < a_{12}x_2^* + a_{13}x_3^*.$$

Moreover, since $\alpha_6 > 0$ and $\alpha_7 > 0$, we have

$$\begin{aligned} \lambda_2 < 0,\ \lambda_3 < 0 \quad &\iff \quad (1 - a_{23}a_{32})\alpha_7 + \eta(\frac{x_2^*}{x_3^*} + a_{23}) > 0 \\ &\iff \quad (1 - a_{23}a_{32}) + \frac{\eta}{\beta_3\theta_3 x_3^*}(\frac{x_2^*}{x_3^*} + a_{23})(\theta_3 + a_{32}x_2^* + x_3^*)^2 > 0. \end{aligned}$$

Thus, E_{23} is asymptotically stable if and only if (3.45) is satisfied.

(6) For the steady state $E_{123} = (x_1^*, x_2^*, x_3^*)$, the characteristic equation for (3.37) is given by (3.38).

From the Routh-Hurwitz stability criterion, all eigenvalues have negative real parts if and only if $a > 0$, $ab - c > 0$ and $c > 0$. Hence, E_{123} is asymptotically stable if and only if (3.46) is satisfied.

Let

$$\alpha_1 = \frac{\beta_1\theta_1 x_1^*}{(\theta_1 + c_1^*)^2},\ \alpha_2 = \frac{\beta_2\theta_2 x_2^*}{(\theta_2 + c_2^*)^2},\ \alpha_3 = \frac{\beta_3\theta_3 x_3^*}{(\theta_3 + c_3^*)^2},$$

and applying (3.31), the coefficient matrix of (3.37) at E_{123} is given by

$$J_{E_{13}} = \begin{pmatrix} -\alpha_1 & -a_{12}\alpha_1 & -a_{13}\alpha_1 \\ -a_{21}\alpha_2 & -\alpha_2 & -a_{23}\alpha_2 \\ -a_{31}\alpha_3 & -a_{32}\alpha_3 + \eta & -\alpha_3 - \eta\dfrac{x_2^*}{x_3^*} \end{pmatrix}. \tag{3.55}$$

Since $\alpha_1, \alpha_2, \alpha_3, x_2^*, x_3^* > 0$, we have

$$a = \alpha_1 + \alpha_2 + \alpha_3 + \eta\frac{x_2^*}{x_3^*} > 0.$$

When the conditions in (3.47) are satisfied, we have

$$1 - a_{23}a_{32} - a_{12}a_{21} - a_{13}a_{31} + a_{13}a_{21}a_{32} + a_{12}a_{23}a_{31} > 0,\ 1 - a_{12}a_{21} > 0,\ a_{23} - a_{13}a_{21} \geqslant 0,$$

and hence

$$\begin{aligned} c &= -\alpha_1(-a_{23}\alpha_2(\eta - a_{32}\alpha_3) - \alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*})) - a_{12}\alpha_1(a_{21}\alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) - a_{23}\alpha_2 a_{31}\alpha_3) \\ &\quad - a_{13}\alpha_1[a_{31}\alpha_2\alpha_3 + a_{21}\alpha_2(\eta - a_{32}\alpha_3)] \\ &= -\alpha_1\Big(- a_{23}\alpha_2(\eta - a_{32}\alpha_3) - \alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + a_{12}(a_{21}\alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) - a_{23}\alpha_2 a_{31}\alpha_3) \\ &\quad + a_{13}(a_{31}\alpha_2\alpha_3 + a_{21}\alpha_2(\eta - a_{32}\alpha_3))\Big) \\ &= \alpha_1\Big((1 - a_{23}a_{32} - a_{12}a_{21} - a_{13}a_{31} + a_{13}a_{21}a_{32} + a_{12}a_{23}a_{31})\alpha_2\alpha_3 \\ &\quad + (a_{23} - a_{21}a_{13})\eta\alpha_2 + (1 - a_{21}a_{12})\eta\alpha_2\frac{x_2^*}{x_3^*}\Big) \\ &> 0. \end{aligned}$$

Furthermore, since

$$2 - a_{13}a_{21}a_{32} - a_{12}a_{23}a_{31} \geqslant 0,\ 1 - a_{23}a_{32} \geqslant 0,\ 1 - a_{12}a_{21} > 0,\ 1 - a_{13}a_{31} \geqslant 0,$$

we have

$$\begin{aligned} ab - c &= \alpha_1^2\alpha_2 + \alpha_1^2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) - a_{12}a_{21}\alpha_1^2\alpha_2 - a_{13}a_{31}\alpha_1^2\alpha_3 + \alpha_2^2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + \alpha_1\alpha_2^2 \\ &\quad + \alpha_1\alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + a_{23}\alpha_2^2(\eta - a_{32}\alpha_3) - a_{12}a_{21}\alpha_1\alpha_2^2 + \alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*})^2 \end{aligned}$$

$$
\begin{aligned}
&+ \alpha_1\alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + \alpha_1(\alpha_3 + \eta\frac{x_2^*}{x_3^*})^2 + a_{23}\alpha_2(\eta - a_{32}\alpha_3)(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) \\
&- a_{13}a_{31}\alpha_1\alpha_3(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + a_{13}a_{21}\alpha_1\alpha_2(\eta - a_{32}\alpha_3) - a_{12}a_{31}a_{23}\alpha_1\alpha_2\alpha_3 \\
= \;& \alpha_1^2\alpha_2 - a_{12}a_{21}\alpha_1^2\alpha_2 + \alpha_1^2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) - a_{13}a_{31}\alpha_1^2\alpha_3 + \alpha_1\alpha_2^2 - a_{12}a_{21}\alpha_1\alpha_2^2 \\
&+ \alpha_2^2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + a_{23}\alpha_2^2(\eta - a_{32}\alpha_3) + \alpha_1(\alpha_3 + \eta\frac{x_2^*}{x_3^*})^2 - a_{13}a_{31}\alpha_1\alpha_3(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) \\
&+ 2\alpha_1\alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) + a_{13}a_{21}\alpha_1\alpha_2(\eta - a_{32}\alpha_3) - a_{12}a_{31}a_{23}\alpha_1\alpha_2\alpha_3 \\
&+ \alpha_2(\alpha_3 + \eta\frac{x_2^*}{x_3^*})^2 + a_{23}\alpha_2(\eta - a_{32}\alpha_3)(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) \\
= \;& (1 - a_{12}a_{21})\alpha_1^2\alpha_2 + (1 - a_{13}a_{31})\alpha_1^2\alpha_3 + \alpha_1^2\eta\frac{x_2^*}{x_3^*} + (1 - a_{12}a_{21})\alpha_1\alpha_2^2 \\
&+ (1 - a_{23}a_{32})\alpha_2^2\alpha_3 + \eta\alpha_2^2\frac{x_2^*}{x_3^*} + a_{23}\eta\alpha_2^2 + (1 - a_{13}a_{31})\alpha_1\alpha_3(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) \\
&+ \alpha_1\eta(\alpha_3 + \eta\frac{x_2^*}{x_3^*})\frac{x_2^*}{x_3^*} + (2 - a_{13}a_{21}a_{32} - a_{12}a_{31}a_{23})\alpha_1\alpha_2\alpha_3 \\
&+ (2\frac{x_2^*}{x_3^*} + a_{13}a_{21})\eta\alpha_1\alpha_2 + (1 - a_{23}a_{32})\alpha_2\alpha_3(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) \\
&+ (\eta\alpha_2\frac{x_2^*}{x_3^*} + a_{23}\eta\alpha_2)(\alpha_3 + \eta\frac{x_2^*}{x_3^*}) \\
> \;& 0.
\end{aligned}
$$

Hence, from the Routh-Hurwitz stability criterion, E_{123} is asymptotically stable.

Theorem 3 gives the conditions for the asymptotical stability of steady states of different types. Specifically, the zero steady state E_0 is asymptotically stable if none of the biological restrictions (2.4)–(2.6) holds, *i.e.*, there is no steady state with non-zero cell numbers. When (2.4)–(2.6) are satisfied, and the competition coefficients $a_{ij} = 0$ $(i \neq j)$, the steady state $E_{123} = (x_1^*, x_2^*, x_3^*)$ exists, and is asymptotically stable, however other nonnegative steady states (E_1, E_3, E_{13} and E_{23}) are unstable. The steady state E_{123} becomes unstable when the competition coefficients increase, and other corresponding nonnegative steady states become stable.

3.3. Therapy strategy

Now, we consider the problem of optimal therapy strategy when both drug-sensitive and drug-resistant tumor cells are co-existence. To this end, we extend the model to include the effect of drug-induced tumor cell death and transition. Here, we consider the possible combination therapy with two drugs, targeted to sensitive cells and resistant cells, respectively. Thus, we introduce the parameters u and v to represent the extra removal rates of drug-sensitive and drug-resistant cells due to treatment stress, respectively. In addition, we assume that the drug targeted to sensitive cells can induce transitions from sensitive cells to resistant cells, the transition rate is represented as su. Thus,

the model (2.2) is modified as

$$\begin{cases} \dfrac{dx_1}{dt} = \beta_1 \dfrac{\theta_1}{\theta_1 + c_1} x_1 - \mu_1 x_1, \\ \dfrac{dx_2}{dt} = (\beta_2 \dfrac{\theta_2}{\theta_2 + c_2} + \beta_{20}) x_2 - \mu_2 x_2 - \eta x_2 - u x_2, \\ \dfrac{dx_3}{dt} = (\beta_3 \dfrac{\theta_3}{\theta_3 + c_3} + \beta_{30}) x_3 - \mu_3 x_3 + \eta x_2 + s u x_2 - v x_3. \end{cases} \tag{3.56}$$

Next we discuss the optimal therapy strategies based on (3.56) by designing the objective functionals with quadratic and linear controls, respectively.

3.3.1. Quadratic control

Firstly, we analyze the quadratic control problem, and study the existence and uniqueness of optimal solutions. In cancer therapy, we try to minimize the total quantity of drugs and the tumor burden during treatment, and hence the associated objective functional can be defined as

$$J(u, v) = \int_0^{t_f} (b(x_2(t) + x_3(t)) + cu(t)^2 + dv(t)^2) dt, \tag{3.57}$$

where t_f denotes the duration of treatment, and $b > 0, c, d$ are constants, which represent non-negative weights of the three parts. Thus, the optimization problem is formulated as

$$\begin{aligned} &\min_{(u,v)\in\mathscr{A}} J(u, v) \\ &\text{s.t.} \begin{cases} \dfrac{dx_1}{dt} = \beta_1 \dfrac{\theta_1}{\theta_1 + c_1} x_1 - \mu_1 x_1, \\ \dfrac{dx_2}{dt} = (\beta_2 \dfrac{\theta_2}{\theta_2 + c_2} + \beta_{20}) x_2 - \mu_2 x_2 - \eta x_2 - u x_2, & t \geqslant 0; \\ \dfrac{dx_3}{dt} = (\beta_3 \dfrac{\theta_3}{\theta_3 + c_3} + \beta_{30}) x_3 - \mu_3 x_3 + \eta x_2 + s u x_2 - v x_3. \end{cases} \\ &(x_1(0), x_2(0), x_3(0)) = (x_{10}, x_{20}, x_{30}) \in \Omega, \\ &\mathscr{A} = \{(u, v) \in L^1[0, t_f] | 0 \leqslant u(t) \leqslant u_{\max}, 0 \leqslant v(t) \leqslant v_{\max}, \forall t \in [0, t_f]\}. \end{aligned} \tag{3.58}$$

Now, we prove the existence of the solution for the optimal control of (3.58).

Theorem 4. *There exists at least one pair of optimal control* (u^*, v^*) *such that*

$$J(u^*, v^*) = \min_{(u,v)\in\mathscr{A}} J(u, v).$$

Proof. First, we show properties below for the control problem (3.57).

(1). First, similar to the argument in Theorem 1, any solutions of (2.2) with initial condition in Ω_1 is bounded with $(x_1(t), x_2(t), x_3(t)) \in \Omega_1$ for any $t > 0$. From the Carathéodory Theorem (Theorem 5.1 in chapter I.5 of [42]), there exist $(x_{10}, x_{20}, x_{30}) \in \Omega_1$ and $(u, v) \in \mathscr{A}$ so that the solution of Eq (3.56) with initial condition $(x_1(0), x_2(0), x_3(0)) = (x_{10}, x_{20}, x_{30})$ is well defined in the interval $[0, t_f]$.

(2). Since the intervals $[0, u_{\max}]$ and $[0, v_{\max}]$ are closed and convex, the admissible control set $\mathscr{A}$ is also closed and convex.

(3). The the right hand side of (3.56) is continuous. Moreover, we can write the right hand side as

$$\zeta_1(x_1, x_2, x_3) + \zeta_2(x_1, x_2, x_3) \cdot \begin{pmatrix} u \\ v \end{pmatrix},$$

where

$$\zeta_1(x_1, x_2, x_3) = \begin{pmatrix} \beta_1 \dfrac{\theta_1}{\theta_1 + c_1} x_1 - \mu_1 x_1 \\ (\beta_2 \dfrac{\theta_2}{\theta_2 + c_2} + \beta_{20}) x_2 - \mu_2 x_2 - \eta x_2 \\ (\beta_3 \dfrac{\theta_3}{\theta_3 + c_3} + \beta_{30}) x_3 - \mu_3 x_3 + \eta x_2 \end{pmatrix}, \quad \text{and} \quad \zeta_2(x_1, x_2, x_3) = \begin{pmatrix} 0 & 0 \\ -x_2 & 0 \\ s x_2 & -x_3 \end{pmatrix}.$$

Since $(x_1, x_2, x_3) \in \Omega_1$ is bounded, there exists $K > 0$ so that

$$\|\zeta_1(x_1, x_2, x_3)\| \leq K\|x\|, \quad \|\zeta_2(x_1, x_2, x_3)\| \leq K.$$

Thus,

$$\left\| \zeta_1(x_1, x_2, x_3) + \zeta_2(x_1, x_2, x_3) \cdot \begin{pmatrix} u \\ v \end{pmatrix} \right\| \leq K(\|x\| + \|(u, v)\|).$$

(4). It is easy to verify that $L = b(x_2(t) + x_3(t)) + cu(t)^2 + dv(t)^2$ is convex with respect to u and v. Moreover, let $c_1 = \min\{c, d\}$, $\beta = 2$, we have

$$L \geqslant c_1 \|(u, v)\|_2^{\beta}.$$

Finally, the existence of the optimal control (u^*, v^*) is followed from the above properties and Corollary 4.1 in [43].

Now, we try to solve the optimal control solution (u^*, v^*). To this end, applying the Pontryagin's maximum(or minimum) principle (PMP), the associated Hamiltonian H is defined as

$$\begin{aligned} H(x_1, x_2, x_3, u, v, \lambda_1, \lambda_2, \lambda_3) \;=\; & b(x_2 + x_3) + cu^2 + dv^2 \\ & + \lambda_1(\beta_1 \frac{\theta_1}{\theta_1 + c_1} - \mu_1)x_1 + \lambda_2(\beta_2 \frac{\theta_2}{\theta_2 + c_2} + \beta_{20} - \mu_2 - \eta - u)x_2 \\ & + \lambda_3(\beta_3 \frac{\theta_3}{\theta_3 + c_3} + \beta_{30})x_3 - \mu_3 x_3 + \eta x_2 + sux_2 - vx_3). \end{aligned} \tag{3.59}$$

Therewith, the associated co-state equations are

$$\begin{cases} \dfrac{d\lambda_1}{dt} = -\dfrac{\partial H}{\partial x_1} = -[\lambda_1(\beta_1 \dfrac{\theta_1}{\theta_1 + c_1} - \mu_1 - \gamma_1) - \lambda_2 a_{21}\gamma_2 - \lambda_3 a_{31}\gamma_3], \\ \dfrac{d\lambda_2}{dt} = -\dfrac{\partial H}{\partial x_2} = -[b - \lambda_1 a_{12}\gamma_1 + \lambda_2(\beta_2 \dfrac{\theta_2}{\theta_2 + c_2} + \beta_{20} - \mu_2 - \eta - u - \gamma_2) + \lambda_3(\eta + su - a_{32}\gamma_3)], \\ \dfrac{d\lambda_3}{dt} = -\dfrac{\partial H}{\partial x_3} = -[b - \lambda_1 a_{13}\gamma_1 - \lambda_2 a_{23}\gamma_2 + \lambda_3(\beta_3 \dfrac{\theta_3}{\theta_3 + c_3} + \beta_{30} - \mu_3 - v - \gamma_3)], \end{cases} \tag{3.60}$$

here,

$$\gamma_1 = \frac{\beta_1 \theta_1 x_1}{(\theta_1 + c_1)^2}, \; \gamma_2 = \frac{\beta_2 \theta_2 x_2}{(\theta_2 + c_2)^2}, \; \gamma_3 = \frac{\beta_3 \theta_3 x_3}{(\theta_3 + c_3)^2},$$

and the associated transversality conditions are

$$\lambda_1(t_f) = 0, \quad \lambda_2(t_f) = 0, \quad \lambda_1(t_f) = 0.$$

On the interior of the control set $\mathscr{A}$, the optimal controls satisfy the condition

$$\frac{\partial H}{\partial u} = \frac{\partial H}{\partial v} = 0.$$

Furthermore, a standard optimality technique implies the optimal controls are given by

$$u^*(t) = \max\left\{0, \min\{u_{\max}, \frac{(\lambda_2(t) - s\lambda_3(t))x_2(t)}{2c}\}\right\} \tag{3.61}$$

and

$$v^*(t) = \max\left\{0, \min\{v_{\max}, \frac{\lambda_3(t)x_3(t)}{2d}\}\right\}. \tag{3.62}$$

Now, analogous to the discussions in previous studies [29, 30, 34], we consider the uniqueness of the optimal control problem. Similar to the argument in Theorem 1, the state variables (x_1, x_2, x_3) of (3.56) are bounded, and there exists an invariant set Ω_1 for the Eq (3.56) with

$$\Omega_1 = \{(x_1, x_2, x_3) \in \mathbb{R}^3 \mid 0 \leqslant x_1 \leqslant b_1, 0 \leqslant x_2 \leqslant b_2, 0 \leqslant x_3 \leqslant b_3\}, \tag{3.63}$$

where $b_1, b_2, b_3 > 0$. Moreover, the solutions of the co-state system (3.60) are bounded with $t \in (0, t_f)$.

Theorem 5. *There exists a sufficiently small final time t_f such that the optimal control solution is unique.*

Proof. We assume that there are two different solutions $(x_1, x_2, x_3, \lambda_1, \lambda_2, \lambda_3)$ and $(\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3)$ that solve (3.56) and (3.60), and will come out with a contradiction.

For a given positive parameter $m > 0$ (to be determined latter), set

$$p_i(t) = x_i(t)e^{-mt}, \quad q_i(t) = \lambda_i(t)e^{mt}, \quad \bar{p}_i(t) = \bar{x}_i(t)e^{-mt}, \quad \bar{q}_i(t) = \bar{\lambda}_i(t)e^{mt}, \quad i = 1, 2, 3.$$

The optimal control solutions $u(t), v(t), \bar{u}(t), \bar{v}(t)$ are given by $p_i(t), q_i(t), \bar{p}_i(t), \bar{q}_i(t)$ as

$$\begin{aligned} u(t) &= \max\left\{0, \min\{u_{\max}, \frac{(q_2(t) - sq_3(t))p_2(t)}{2c}\}\right\}, \qquad v(t) = \max\left\{0, \min\{v_{\max}, \frac{q_3(t)p_3(t)}{2d}\}\right\}, \\ \bar{u}(t) &= \max\left\{0, \min\{u_{\max}, \frac{(\bar{q}_2(t) - s\bar{q}_3(t))\bar{p}_2(t)}{2c}\}\right\}, \qquad \bar{v}(t) = \max\left\{0, \min\{v_{\max}, \frac{\bar{q}_3(t)\bar{p}_3(t)}{2d}\}\right\}. \end{aligned} \tag{3.64}$$

Substituting $x_i(t) = p_i(t)e^{mt}, \lambda_i(t) = q_i(t)e^{-mt}$ into Eqs (3.56) and (3.60), after a tedious calculation (see the Appendix), we obtain that there exist $L_{1,i} > 0, L_{2,i} > 0$ so that

$$m\int_0^{t_f}(p_i - \bar{p}_i)^2 dt \leqslant L_{1,i}(1 + e^{mt_f})\int_0^{t_f}\left(\sum_{j=1}^{3}((\bar{p}_j - p_j)^2 + (\bar{q}_j - q_j)^2)\right)dt, \tag{3.65}$$

and

$$m\int_0^{t_f}(q_i - \bar{q}_i)^2 dt \leqslant L_{2,i}(1 + e^{mt_f} + e^{2mt_f} + e^{3mt_f})\int_0^{t_f}\left(\sum_{j=1}^{3}((\bar{p}_j - p_j)^2 + (\bar{q}_j - q_j)^2)\right)dt. \tag{3.66}$$

Thus, adding up (3.65) and (3.66) for $i = 1, 2, 3$, there exists $L_3 = \max_{i=1,2,3}\{L_{1,i} + L_{2,i}\}$ so that

$$(m - L_3(1 + e^{mt_f} + e^{2mt_f} + e^{3mt_f})) \int_0^{t_f} \left(\sum_{j=1}^{3} ((\bar{p}_j - p_j)^2 + (\bar{q}_j - q_j)^2) \right) dt \leqslant 0, \tag{3.67}$$

and L_3 only depends on all equation coefficients.

Now, while we choose $m = L_3(1 + 3e)$ and $t_f < \dfrac{1}{3m}$, then $m - L(1 + e^{mt_f} + e^{2mt_f} + e^{3mt_f}) > 0$, which come out with a contradiction with (3.67) if $(p_j, q_j) \neq (\bar{p}_j, \bar{q}_j)$. Thus, we conclude $p_i = \bar{p}_i$ and $q_i = \bar{q}_i$, and hence $u = \bar{u}$ and $v = \bar{v}$ from (3.64).

3.3.2. Linear control

Now, we consider the situation of linear control problem, and seek to minimize the pay-off functional J_1 that is defined as

$$J_1(u, v) = \int_0^{t_f} [b(x_2(t) + x_3(t)) + cu(t) + dv(t)]dt. \tag{3.68}$$

Similar to discussions in Theorem 4, we have the existence of optimal control strategy (u, v) that minimizes $J_1(u, v)$.

Now, the necessary conditions of the above optimal problem can be given by the PMP [44]. According to PMP, the associated Hamiltonian H is written as

$$\begin{aligned} H(x_1, x_2, x_3, u, v, \lambda_1, \lambda_2, \lambda_3) \;=\; & b(x_2 + x_3) + cu + dv \\ & + \lambda_1(\beta_1 \frac{\theta_1}{\theta_1 + c_1} - \mu_1)x_1 + \lambda_2(\beta_2 \frac{\theta_2}{\theta_2 + c_2} + \beta_{20} - \mu_2 - \eta - u)x_2 \\ & + \lambda_3[(\beta_3 \frac{\theta_3}{\theta_3 + c_3} + \beta_{30})x_3 - \mu_3 x_3 + \eta x_2 + sux_2 - vx_3]. \end{aligned} \tag{3.69}$$

Thus, the associated co-state equations are

$$\begin{cases} \dfrac{d\lambda_1}{dt} = -\dfrac{\partial H}{\partial x_1} = -[\lambda_1(\beta_1 \dfrac{\theta_1}{\theta_1 + c_1} - \mu_1 - \gamma_1) - \lambda_2 a_{21}\gamma_2 - \lambda_3 a_{31}\gamma_3], \\ \dfrac{d\lambda_2}{dt} = -\dfrac{\partial H}{\partial x_2} = -[b - \lambda_1 a_{12}\gamma_1 + \lambda_2(\beta_2 \dfrac{\theta_2}{\theta_2 + c_2} + \beta_{20} - \mu_2 - \eta - u - \gamma_2) + \lambda_3(\eta + su - a_{32}\gamma_3)], \\ \dfrac{d\lambda_3}{dt} = -\dfrac{\partial H}{\partial x_3} = -[b - \lambda_1 a_{13}\gamma_1 - \lambda_2 a_{23}\gamma_2 + \lambda_3(\beta_3 \dfrac{\theta_3}{\theta_3 + c_3} + \beta_{30} - \mu_3 - v - \gamma_3)], \end{cases} \tag{3.70}$$

where

$$\gamma_1 = \frac{\beta_1\theta_1 x_1}{(\theta_1 + c_1)^2}, \gamma_2 = \frac{\beta_2\theta_2 x_2}{(\theta_2 + c_2)^2}, \gamma_3 = \frac{\beta_3\theta_3 x_3}{(\theta_3 + c_3)^2},$$

and the associated transversality conditions are

$$\lambda_1(t_f) = 0, \quad \lambda_2(t_f) = 0, \quad \lambda_1(t_f) = 0.$$

The optimal control solution (u, v) satisfies

$$\frac{\partial H}{\partial u} = c - \lambda_2 x_2 + s\lambda_3 x_2, \quad \frac{\partial H}{\partial v} = d - \lambda_3 x_3. \tag{3.71}$$

Hence the optimal control solution is given by

$$u^*(t) = \begin{cases} 0, & c - \lambda_2 x_2 + s\lambda_3 x_2 > 0, \\ u_{\max}, & c - \lambda_2 x_2 + s\lambda_3 x_2 < 0. \end{cases} \tag{3.72}$$

and

$$v^*(t) = \begin{cases} 0, & d - \lambda_3 x_3 > 0, \\ v_{\max}, & d - \lambda_3 x_3 < 0. \end{cases} \tag{3.73}$$

From (3.72) and (3.73), the optimal controls for the linear problem is a bang-bang control with either zero or maximum dose drugs.

3.3.3. Numerical results

Now, we perform numerical simulations to verify the above analytic discussions. To carry out the numerical simulation, firstly we need to specify parameter values in our model. Since our model is proposed to describe the dynamics of tumor growth with both drug-sensitive and drug-resistant cells, we assume that the proliferation rate of drug-sensitive cancer cells is larger than that of normal cells, and the self-sustained growth rates of cancer cells are nonzero. Moreover, the proliferation rate of drug-resistant cells is larger than that of sensitive cells, but sensitive cells can strongly inhibit the proliferation of drug-resistant cells. Thus, we should have

$$\beta_3 > \beta_2 > \beta_1,\ \beta_{20} > 0,\ \beta_{30} > 0,\ a_{32} > 1.$$

Different types of cells response differently to the cytokines, and hence we assume that θ_i can be different for different types of cells. Default parameter values used in numerical simulation are listed in the Table 1. Figure 2(a) shows the cell number dynamics in the case without treatment, in which the system states (x_1, x_2, x_3) approaches the steady state of E_{123}-type. At this state, drug-sensitive cells are dominant in the system, and there are a small fraction of pre-existing drug-resistant cells.

Now, we consider the effect of sequential treatment, with only one drug at one period. To this end, we run the model Eq (3.56) with $u = v = 0$ to $t = 200$ days so that cancer cells numbers reach a high level near the steady state. Next, we set $u = u_{\max}$ to turn on the drug targeted to sensitive cells (u-drug for short) for 200 days. Then, we set $u = 0$ and $v = v_{\max}$ to turn on the drug targeted to resistant cells (v-drug for short). Figure 2(b) shows the cell number dynamics after sequential treatment. From Figure 2(b), after the administration of u-drug, sensitive cell numbers rapidly decreases to an extreme low level, however resistant cells number increases to a high level and becomes dominant. Next, after the administration of v-drug, resistant cells number decreases, and sensitive cells number increases again, which show the clinical symptom of tumor relapse.

Table 1. Default parameter values.

Parameter	Value	Unit
β_1	0.85	day^{-1}
β_2	1.1	day^{-1}
β_3	1.2	day^{-1}
θ_1	45.0	$\times 10^6$cells
θ_2	96.0	$\times 10^6$cells
θ_3	60.0	$\times 10^6$cells
β_{20}	0.0002	day^{-1}
β_{30}	0.0002	day^{-1}
μ_1	0.05	day^{-1}
μ_2	0.05	day^{-1}
μ_3	0.05	day^{-1}
η	0.0002	day^{-1}
a_{12}	0.16	-
a_{13}	0.44	-
a_{21}	0.46	-
a_{23}	0.38	-
a_{31}	0.57	-
a_{32}	1.2	-
$u_{\max}$	0.24	day^{-1}
$v_{\max}$	0.3	day^{-1}
s	0.002	-
b	1	-
c	70	-
d	0.15	-

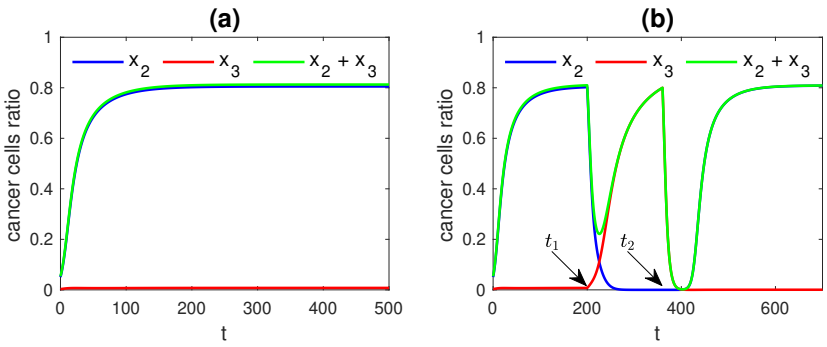

Figure 2. Evolution of cell counts. (a) Cell count dynamics with no treatment. (b) Cell count dynamics under sequential treatment with two drugs. Here, the u-drug and v-drug are administrated in the time interval of $t \in [t_1, t_2]$ and $t \in [t_2, 700]$, respectively. In all simulations, initial conditions are $x_{10} = 600, x_{20} = 32, x_{30} = 2$, and parameters are taken from Table 1.

Now, we investigate the dynamics of cell number ratios under different treatment strategies with either u-drug or v-drug alone, or sequential treatment with the two drugs. Here, the drug is applied at $t = 200$ as in Figure 2 by which sensitive cells are dominant. After the administration of u-drug for 60 days, the ratio of sensitive cells decrease over time, however the ratio of resistant cells increase along with treatment, and the ratio of total cancer cells slowly increases following the decreasing phase in the early stage after treatment (Figure 3(a),(b)). If v-drug is applied alone, there is no obvious decreases in the cancer cells ratio after treatment (Figure 3(c),(d)). The reason is obvious, since the v-drug targeted cells contribute only a small fraction of cancer cells before treatment. Finally, in the case with sequential treatment of two drugs, the total cancer cells ratio shows continuous decrease over time, and reaches a level below 0.2 after 60 days treatment (Figure 3). These results suggest that various treatment strategies can result in different outcomes.

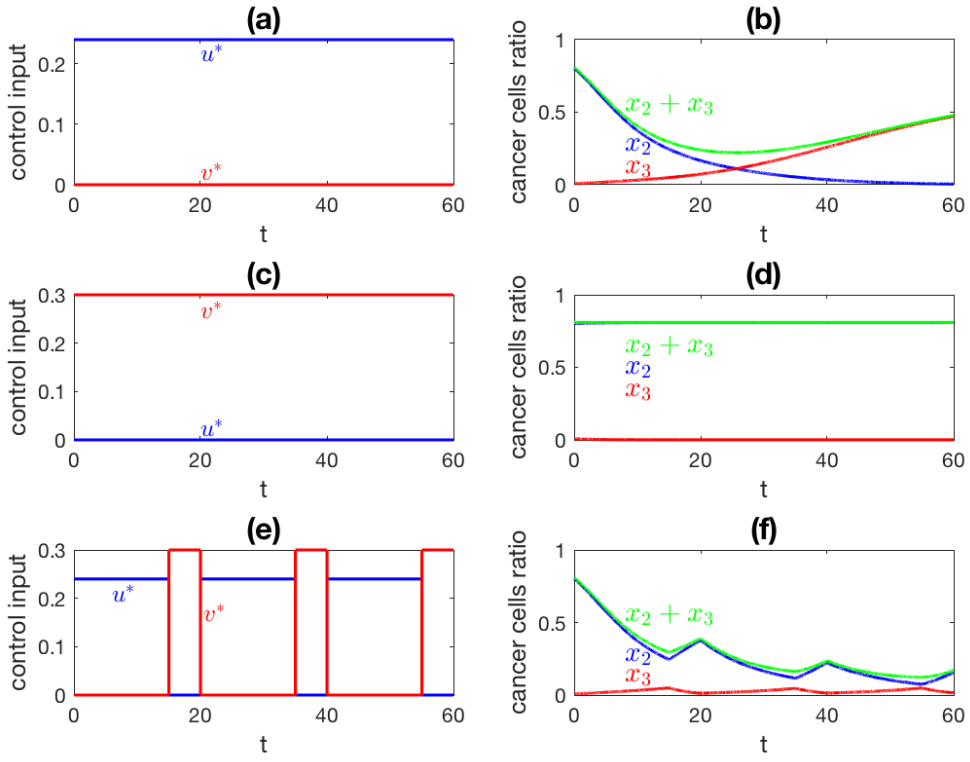

Figure 3. Dynamics of cancer cells ratio under different treatment strategies. (a) Treatment strategy with continuous u-drug. (b) Dynamics of cancer cells ratio corresponding to the strategy (a). (c) Treatment strategy with continuous v-drug. (d) Dynamics of cancer cells ratio corresponding to the strategy (c). (e) Treatment strategy with sequential treatment with u-drug and v-drug. (f) Dynamics of cancer cells ratio corresponding to the strategy (e). Parameters are taken from Table 1.

To investigate the effect of optimal control strategy, we numerically solve the optimal control problem with the method of forward-backward sweep method (FBSM) [45]. Figure 4 shows the result corresponding to the quadratic control problem. Here, we take the weight coefficients $b = 1$, $c = 70$ and $d = 0.15$ (Table 1). The optimal solution in Figure 4 suggests that we should apply the maximum

dose drugs simultaneously, and continuously reduce the drug doses at the end point of treatment. In this case, the total cancer cells ratio continuously decreases toward a level (2.93%) much lower than those in Figure 3.

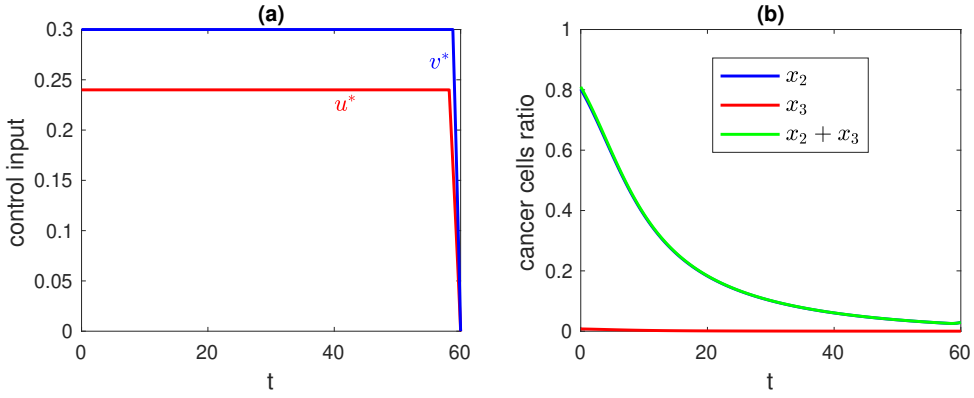

Figure 4. Optimal solution of quadratic control problem. (a) Drug doses corresponding to the optimal solution of the quadratic control problem. (b) Cancer cells ratio corresponding to the optimal solution in (a). Parameters are taken from Table 1.

In the Eq (3.56), we introduce a parameter s to represent the effect of transition from sensitive cells to resistant cells. Biologically, the transition can be induced by epigenetic, adaptive changes, or gene mutation due to drug stress. To investigate how the transition may affect the optimal control treatment, we vary the relative strength of the transition rate (measured by the ratio $su_{\max}/\eta$), and calculate the total drug doses

$$U(t) = \int_0^{t_f} u(t)dt, V(t) = \int_0^{t_f} v(t)dt, \tag{3.74}$$

and the ratio of cancer cells at $t = 60$ for each value $su_{\max}$. Results show that both total doses and the ratio of cancer cells are insensitive with changes in the relative strength of the transition rate (Figure 5).

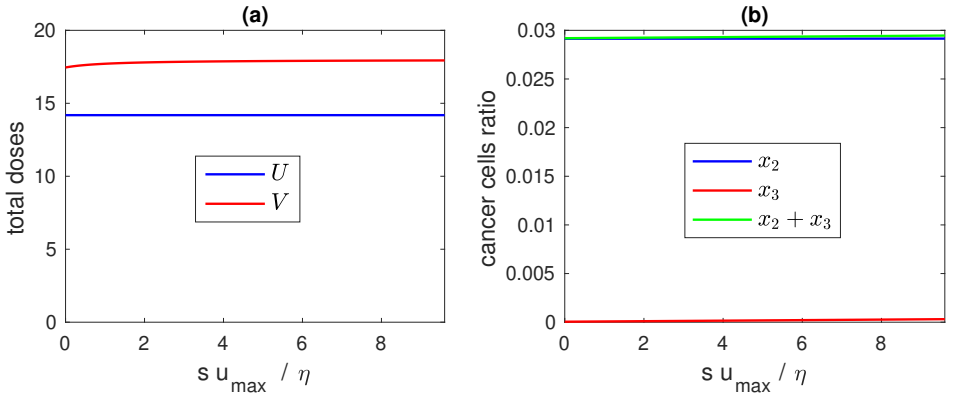

Figure 5. Optimal solutions of quadratic control with different values $su_{\max}/\eta$. (a) Total drug doses defined by (3.74) during treatment versus su_{max}/η. (b) Cancer cells ratio at $t = 60$ versus $su_{\max}/\eta$. Here, other parameters are taken from Table 1.

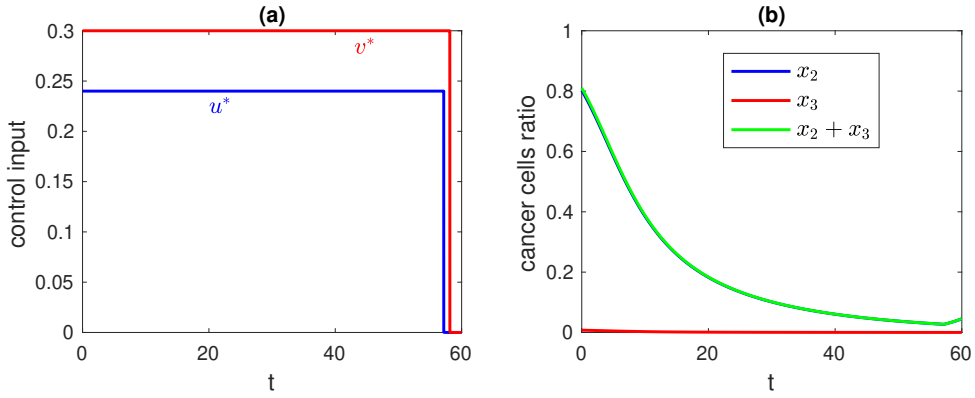

Figure 6. Optimal solution of linear control problem. (a) Drug doses corresponding to the optimal solution of the linear control problem. (b) Cancer cells ratio corresponding to the optimal solution in (a). Parameters are taken from Table 1.

Similarly, we solve the optimal control problem with linear control pay-off functional, which yields a bang-bang control. We obtain similar optimal solutions as in the case of quadratic control, in which both drugs are administrated simultaneously with maximum doses, and stop the treatment at later stage (Figure 6). Correspondingly, the final total cancer cells ratio at $t = 60$ decreases to about 4.54%. Moreover, we vary the relative strength of the transition rate $su_{\max}/\eta$ to examine the dependences of the total drug doses and final cancer ratios on the relative strength of the transition rate $su_{\max}/\eta$. Similar to the situation of quadratic control problem, both the total drug doses and final cancer cells ratio are nonsensitive with the transition rate $su_{\max}/\eta$ (Figure 7).

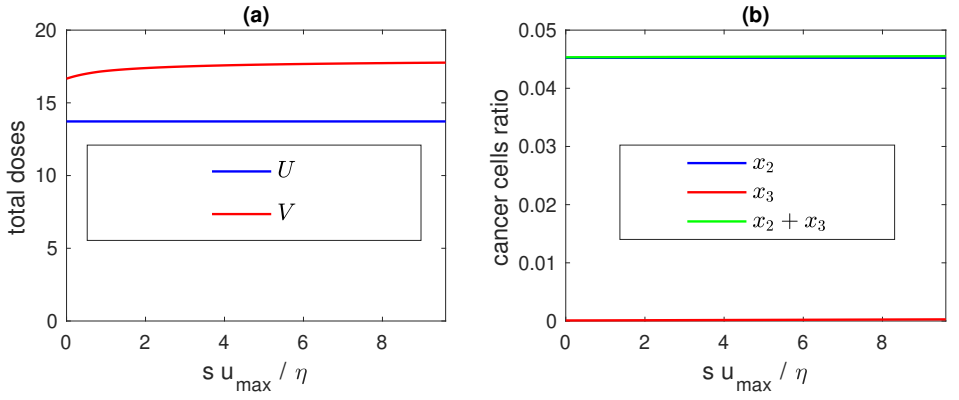

Figure 7. Optimal solutions of linear control problem with different values $su_{\max}/\eta$. (a) Total drug doses defined by (3.74) during treatment versus $su_{\max}/\eta$. (b) Cancer cells ratio at $t = 60$ versus $su_{\max}/\eta$. Here, other parameters are taken from Table 1.

4. Conclusions

Intratumor heterogeneity is important to cell competition, and may play important roles in cancer evolution. Here, we study a mathematical model of cancer evolution that includes competition between normal cells and two types of cancer cells, as well as the transition between cancer cells. Moreover, the potential transition from drug-sensitive cancer cells to drug-resistant cancer cells is also involved

in the model. Based on the model, the invariant set of the nonnegative solutions, and the existence and the stability of steady sates are discussed. We further discuss the optimal control problem that trying to find the treatment strategy to minimize the optimal functional for both tumor burden and drug doses. We prove the existence and uniqueness of the optimal control strategy for the proposed model. Finally, numerical simulations are performed to verify the optimal control solutions.

In the present study, we study the problem of optimal treatment strategy of cancer through a simple differential equation model. This model considers the competition between different types of cells. In the realistic world, optimal treatment of cancer relies on two techniques: (1) effective method to measure the state of tumor growth; (2) reliable prediction of tumor growth. However, neither of these two techniques are available at present, and there is still a long way toward real world application of the concept of optimal control treatment. This paper is rather a conceptual study that try to explore the possible cell population dynamics when there are competitions between different types of cells, and the possible benefit of optimal treatment in comparing with traditional maximum dose treatment (MDT). The current study is based on a toy model of cell competitions in which different types of cells are assumed to be homogeneous, and the effects of microenvironment are not included in the model, the immune response are not included explicitly. To develop a more realistic and applicable model, these factors are for sure to be included, which is a big ambition in the field of computational cancer biology.

Acknowledgments

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Conflict of interest

The authors declare there is no conflict of interest.

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Appendix

Proof of the inequalities (3.65) ***and*** (3.66)

Substituting $x_i(t) = p_i(t)e^{mt}, \lambda_i(t) = q_i(t)e^{-mt}$ into equations (3.56) and (3.60), we have (hereafter, $\dot{}$ means $\frac{d}{dt}$)

$$\begin{aligned}
\dot{p}_1e^{mt} + mp_1e^{mt} &= \frac{\beta_1\theta_1e^{mt}p_1}{\theta_1 + e^{mt}p_1 + a_{12}e^{mt}p_2 + a_{13}e^{mt}p_3} - \mu_1e^{mt}p_1,\\
\dot{p}_2e^{mt} + mp_2e^{mt} &= \frac{\beta_2\theta_2e^{mt}p_2}{\theta_2 + a_{21}e^{mt}p_1 + e^{mt}p_2 + a_{23}e^{mt}p_3} + (\beta_{20} - \mu_2 - \eta)e^{mt}p_2 - ue^{mt}p_2,\\
\dot{p}_3e^{mt} + mp_3e^{mt} &= \frac{\beta_3\theta_3e^{mt}p_3}{\theta_3 + a_{31}e^{mt}p_1 + a_{32}e^{mt}p_2 + e^{mt}p_3} + (\beta_{30} - \mu_3)e^{mt}p_3 + \eta e^{mt}p_2 + sue^{mt}p_2 - ve^{mt}p_3,
\end{aligned}$$

and

$$\begin{aligned}
\dot{q}_1e^{-mt} - mq_1e^{-mt} &= -\frac{\beta_1\theta_1e^{-mt}q_1}{\theta_1 + e^{mt}p_1 + a_{12}e^{mt}p_2 + a_{13}e^{mt}p_3} + \mu_1e^{-mt}q_1\\
&\quad + \frac{\beta_1\theta_1e^{mt}p_1e^{-mt}q_1}{(\theta_1 + e^{mt}p_1 + a_{12}e^{mt}p_2 + a_{13}e^{mt}p_3)^2} + \frac{a_{21}\beta_2\theta_2e^{mt}p_2e^{-mt}q_2}{(\theta_2 + a_{21}e^{mt}p_1 + e^{mt}p_2 + a_{23}e^{mt}p_3)^2}
\end{aligned}$$

$$
\begin{aligned}
&+\frac{a_{31}\beta_3\theta_3 e^{mt}p_3e^{-mt}q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2},\\
\dot{q}_2e^{-mt}-mq_2e^{-mt} &= -b+\frac{a_{12}\beta_1\theta_1e^{mt}p_1e^{-mt}q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}+(\mu_2+\eta-\beta_{20})e^{-mt}q_2+e^{-mt}uq_2\\
&-\frac{\beta_2\theta_2e^{-mt}q_2}{\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3}+\frac{\beta_2\theta_2e^{mt}p_2e^{-mt}q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}\\
&+\frac{a_{32}\beta_3\theta_3e^{mt}p_3e^{-mt}q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}-\eta e^{-mt}q_3-se^{-mt}uq_3,\\
\dot{q}_3e^{-mt}-mq_3e^{-mt} &= -b+\frac{a_{13}\beta_1\theta_1e^{mt}p_1e^{-mt}q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}\\
&+\frac{a_{23}\beta_2\theta_2e^{mt}p_2e^{-mt}q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}-\frac{\beta_3\theta_3e^{-mt}q_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}\\
&+(\mu_3-\beta_{30})e^{-mt}q_3+e^{-mt}vq_3+\frac{\beta_3\theta_3e^{mt}p_3e^{-mt}q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}.
\end{aligned}
$$

Multiplying both sides of the first three equation by e^{-mt}, and the last three equations by e^{mt}, respectively, we obtain

$$
\begin{aligned}
\dot{p}_1+mp_1 &= \frac{\beta_1\theta_1p_1}{\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3}-\mu_1p_1,\\
\dot{p}_2+mp_2 &= \frac{\beta_2\theta_2p_2}{\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3}+(\beta_{20}-\mu_2-\eta)p_2-up_2,\\
\dot{p}_3+mp_3 &= \frac{\beta_3\theta_3p_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}+(\beta_{30}-\mu_3)p_3+\eta p_2+sup_2-vp_3,\\
\dot{q}_1-mq_1 &= -\frac{\beta_1\theta_1q_1}{\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3}+\mu_1q_1\\
&+\frac{\beta_1\theta_1e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}+\frac{a_{21}\beta_2\theta_2e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}\\
&+\frac{a_{31}\beta_3\theta_3e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2},\\
\dot{q}_2-mq_2 &= -be^{mt}+\frac{a_{12}\beta_1\theta_1e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}+(\mu_2+\eta-\beta_{20})q_2+uq_2\\
&-\frac{\beta_2\theta_2q_2}{\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3}+\frac{\beta_2\theta_2e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}\\
&+\frac{a_{32}\beta_3\theta_3e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}-\eta q_3-suq_3,\\
\dot{q}_3-mq_3 &= -be^{mt}+\frac{a_{13}\beta_1\theta_1e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}\\
&+\frac{a_{23}\beta_2\theta_2e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}-\frac{\beta_3\theta_3q_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}\\
&+(\mu_3-\beta_{30})q_3+vq_3+\frac{\beta_3\theta_3e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}.
\end{aligned}
$$

Similarly, we obtain the same form equations of $\bar{p}_i$ and $\bar{\lambda}_i$, $i=1,2,3$.

Next, subtracting the equations for p_i and $\bar{p}_i$, and the equations for q_i and $\bar{q}_1$, we have

$$\begin{aligned}
(\dot{p}_1-\dot{\bar{p}}_1)+m(p_1-\bar{p}_1) &= \frac{\beta_1\theta_1 p_1}{\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3}-\frac{\beta_1\theta_1\bar{p}_1}{\theta_1+e^{mt}\bar{p}_1+a_{12}e^{mt}\bar{p}_2+a_{13}e^{mt}\bar{p}_3}\\
&\quad -\mu_1(p_1-\bar{p}_1),\\
(\dot{p}_2-\dot{\bar{p}}_2)+m(p_2-\bar{p}_2) &= \frac{\beta_2\theta_2 p_2}{\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3}-\frac{\beta_2\theta_2\bar{p}_2}{\theta_2+a_{21}e^{mt}\bar{p}_1+e^{mt}\bar{p}_2+a_{23}e^{mt}\bar{p}_3}\\
&\quad +(\beta_{20}-\mu_2-\eta)(p_2-\bar{p}_2)-(up_2-\bar{u}\bar{p}_2),\\
(\dot{p}_3-\dot{\bar{p}}_3)+m(p_3-\bar{p}_3) &= \frac{\beta_3\theta_3 p_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}-\frac{\beta_3\theta_3\bar{p}_3}{\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3}\\
&\quad +(\beta_{30}-\mu_3)(p_3-\bar{p}_3)+\eta(p_2-\bar{p}_2)+s(up_2-\bar{u}\bar{p}_2)-(vp_3-\bar{v}\bar{p}_3),
\end{aligned}$$

and

$$\begin{aligned}
(\dot{q}_1-\dot{\bar{q}}_1)-m(q_1-\bar{q}_1) &= -\frac{\beta_1\theta_1 q_1}{\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3}+\frac{\beta_1\theta_1\bar{q}_1}{\theta_1+e^{mt}\bar{p}_1+a_{12}e^{mt}\bar{p}_2+a_{13}e^{mt}\bar{p}_3}\\
&\quad +\mu_1(q_1-\bar{q}_1)\\
&\quad +\frac{\beta_1\theta_1 e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}-\frac{\beta_1\theta_1 e^{mt}\bar{p}_1\bar{q}_1}{(\theta_1+e^{mt}\bar{p}_1+a_{12}e^{mt}\bar{p}_2+a_{13}e^{mt}\bar{p}_3)^2}\\
&\quad +\frac{a_{21}\beta_2\theta_2 e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}-\frac{a_{21}\beta_2\theta_2 e^{mt}\bar{p}_2\bar{q}_2}{(\theta_2+a_{21}e^{mt}\bar{p}_1+e^{mt}\bar{p}_2+a_{23}e^{mt}\bar{p}_3)^2}\\
&\quad +\frac{a_{31}\beta_3\theta_3 e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}-\frac{a_{31}\beta_3\theta_3 e^{mt}\bar{p}_3\bar{q}_3}{(\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3)^2},\\
(\dot{q}_2-\dot{\bar{q}}_2)-m(q_2-\bar{q}_2) &= \frac{a_{12}\beta_1\theta_1 e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}-\frac{a_{12}\beta_1\theta_1 e^{mt}\bar{p}_1\bar{q}_1}{(\theta_1+e^{mt}\bar{p}_1+a_{12}e^{mt}\bar{p}_2+a_{13}e^{mt}\bar{p}_3)^2}\\
&\quad -\frac{\beta_2\theta_2 q_2}{\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3}+\frac{\beta_2\theta_2\bar{q}_2}{\theta_2+a_{21}e^{mt}\bar{p}_1+e^{mt}\bar{p}_2+a_{23}e^{mt}\bar{p}_3}\\
&\quad +\frac{\beta_2\theta_2 e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}-\frac{\beta_2\theta_2 e^{mt}\bar{p}_2\bar{q}_2}{(\theta_2+a_{21}e^{mt}\bar{p}_1+e^{mt}\bar{p}_2+a_{23}e^{mt}\bar{p}_3)^2}\\
&\quad +\frac{a_{32}\beta_3\theta_3 e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}-\frac{a_{32}\beta_3\theta_3 e^{mt}\bar{p}_3\bar{q}_3}{(\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3)^2}\\
&\quad +(\mu_2+\eta-\beta_{20})(q_2-\bar{q}_2)+uq_2-\bar{u}\bar{q}_2-\eta(q_3-\bar{q}_3)-s(uq_3-\bar{u}\bar{q}_3),\\
(\dot{q}_3-\dot{\bar{q}}_3)-m(q_3-\bar{q}_3) &= \frac{a_{13}\beta_1\theta_1 e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}-\frac{a_{13}\beta_1\theta_1 e^{mt}\bar{p}_1\bar{q}_1}{(\theta_1+e^{mt}\bar{p}_1+a_{12}e^{mt}\bar{p}_2+a_{13}e^{mt}\bar{p}_3)^2}\\
&\quad +\frac{a_{23}\beta_2\theta_2 e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}-\frac{a_{23}\beta_2\theta_2 e^{mt}\bar{p}_2\bar{q}_2}{(\theta_2+a_{21}e^{mt}\bar{p}_1+e^{mt}\bar{p}_2+a_{23}e^{mt}\bar{p}_3)^2}\\
&\quad -\frac{\beta_3\theta_3 q_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}+\frac{\beta_3\theta_3\bar{q}_3}{\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3}\\
&\quad +\frac{\beta_3\theta_3 e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}-\frac{\beta_3\theta_3 e^{mt}\bar{p}_3\bar{q}_3}{(\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3)^2}\\
&\quad +(\mu_3-\beta_{30})(q_3-\bar{q}_3)+vq_3-\bar{v}\bar{q}_3.
\end{aligned}$$

Now, we consider the equations for $(p_3-\bar{p}_3)$ and $(-q_3+\bar{q}_3)$, and other equations can be treated similarly. Multiplying the equation for $(p_3-\bar{p}_3)$ by $(p_3-\bar{p}_3)$, and integrating the obtained equation

from 0 to t_f, we have

$$\begin{aligned}
&\frac{1}{2}(p_3(t)-\bar{p}_3(t))^2\Big|_0^{t_f}+m\int_0^{t_f}(p_3-\bar{p}_3)^2dt\\
=\;&\int_0^{t_f}\Big(\frac{\beta_3\theta_3p_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}-\frac{\beta_3\theta_3\bar{p}_3}{\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3}\Big)(p_3-\bar{p}_3)dt\\
&+(\beta_{30}-\mu_3)\int_0^{t_f}(p_3-\bar{p}_3)^2dt+\eta\int_0^{t_f}(p_2-\bar{p}_2)(p_3-\bar{p}_3)dt\\
&+s\int_0^{t_f}(up_2-\bar{u}\bar{p}_2)(p_3-\bar{p}_3)dt-\int_0^{t_f}(vp_3-\bar{v}\bar{p}_3)(p_3-\bar{p}_3)dt. \qquad (4.1)
\end{aligned}$$

Multiplying the equation for $(q_3-\bar{q}_3)$ by $(-q_3+\bar{q}_3)$, and integrating the obtained equation from 0 to t_f, we have

$$\begin{aligned}
&-\frac{1}{2}(q_3(t)-\bar{q}_3(t))^2\Big|_0^{t_f}+m\int_0^{t_f}(q_3-\bar{q}_3)^2dt\\
=\;&\int_0^{t_f}\Big(\frac{a_{13}\beta_1\theta_1e^{mt}p_1q_1}{(\theta_1+e^{mt}p_1+a_{12}e^{mt}p_2+a_{13}e^{mt}p_3)^2}-\frac{a_{13}\beta_1\theta_1e^{mt}\bar{p}_1\bar{q}_1}{(\theta_1+e^{mt}\bar{p}_1+a_{12}e^{mt}\bar{p}_2+a_{13}e^{mt}\bar{p}_3)^2}\Big)(\bar{q}_3-q_3)dt\\
&+\int_0^{t_f}\Big(\frac{a_{23}\beta_2\theta_2e^{mt}p_2q_2}{(\theta_2+a_{21}e^{mt}p_1+e^{mt}p_2+a_{23}e^{mt}p_3)^2}-\frac{a_{23}\beta_2\theta_2e^{mt}\bar{p}_2\bar{q}_2}{(\theta_2+a_{21}e^{mt}\bar{p}_1+e^{mt}\bar{p}_2+a_{23}e^{mt}\bar{p}_3)^2}\Big)(\bar{q}_3-q_3)dt\\
&-\int_0^{t_f}\Big(\frac{\beta_3\theta_3q_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}-\frac{\beta_3\theta_3\bar{q}_3}{\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3}\Big)(\bar{q}_3-q_3)dt\\
&+\int_0^{t_f}\Big(\frac{\beta_3\theta_3e^{mt}p_3q_3}{(\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3)^2}-\frac{\beta_3\theta_3e^{mt}\bar{p}_3\bar{q}_3}{(\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3)^2}\Big)(\bar{q}_3-q_3)dt\\
&-\int_0^{t_f}(\mu_3-\beta_{30})(q_3-\bar{q}_3)^2dt+\int_0^{t_f}(vq_3-\bar{v}\bar{q}_3)(\bar{q}_3-q_3)dt. \qquad (4.2)
\end{aligned}$$

We note that $p_3(0)=\bar{p}_3(0)=x_{30}$, equation (4.1) implies

$$\begin{aligned}
&\frac{1}{2}(p_3(t_f)-\bar{p}_3(t_f))^2+m\int_0^{t_f}(p_3-\bar{p}_3)^2dt\\
=\;&\int_0^{t_f}\Big(\frac{\beta_3\theta_3p_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}-\frac{\beta_3\theta_3\bar{p}_3}{\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3}\Big)(p_3-\bar{p}_3)dt\\
&+(\beta_{30}-\mu_3)\int_0^{t_f}(p_3-\bar{p}_3)^2dt+\eta\int_0^{t_f}(p_2-\bar{p}_2)(p_3-\bar{p}_3)dt\\
&+s\int_0^{t_f}(up_2-\bar{u}\bar{p}_2)(p_3-\bar{p}_3)dt-\int_0^{t_f}(vp_3-\bar{v}\bar{p}_3)(p_3-\bar{p}_3)dt\\
\leqslant\;&\int_0^{t_f}\Big|\frac{\beta_3\theta_3p_3}{\theta_3+a_{31}e^{mt}p_1+a_{32}e^{mt}p_2+e^{mt}p_3}-\frac{\beta_3\theta_3\bar{p}_3}{\theta_3+a_{31}e^{mt}\bar{p}_1+a_{32}e^{mt}\bar{p}_2+e^{mt}\bar{p}_3}\Big||p_3-\bar{p}_3|dt\\
&+(\beta_{30}-\mu_3)\int_0^{t_f}(p_3-\bar{p}_3)^2dt+\eta\int_0^{t_f}(p_2-\bar{p}_2)(p_3-\bar{p}_3)dt\\
&+s\int_0^{t_f}(up_2-\bar{u}\bar{p}_2)(p_3-\bar{p}_3)dt-\int_0^{t_f}(vp_3-\bar{v}\bar{p}_3)(p_3-\bar{p}_3)dt. \qquad (4.3)
\end{aligned}$$

Since the solutions of (3.56) are nonnegative, namely $p_i, \bar{p}_i \geqslant 0$, we have

$$(\theta_3 + a_{31}e^{mt}p_1 + a_{32}e^{mt}p_2 + e^{mt}p_3)(\theta_3 + a_{31}e^{mt}\bar{p}_1 + a_{32}e^{mt}\bar{p}_2 + e^{mt}\bar{p}_3) \geqslant \theta_3^2.$$

Hence,

$$\begin{aligned}
&\frac{1}{2}(p_3(t_f) - \bar{p}_3(t_f))^2 + m\int_0^{t_f}(p_3 - \bar{p}_3)^2dt \\
\leqslant\ & \frac{\beta_3}{\theta_3}\int_0^{t_f}\Big|p_3(\theta_3 + a_{31}e^{mt}\bar{p}_1 + a_{32}e^{mt}\bar{p}_2 + e^{mt}\bar{p}_3) - \bar{p}_3(\theta_3 + a_{31}e^{mt}p_1 + a_{32}e^{mt}p_2 + e^{mt}p_3)\Big||p_3 - \bar{p}_3|dt \\
&+ (\beta_{30} - \mu_3)\int_0^{t_f}(p_3 - \bar{p}_3)^2dt + \eta\int_0^{t_f}(p_2 - \bar{p}_2)(p_3 - \bar{p}_3)dt \\
&+ s\int_0^{t_f}(up_2 - \bar{u}\bar{p}_2)(p_3 - \bar{p}_3)dt - \int_0^{t_f}(vp_3 - \bar{v}\bar{p}_3)(p_3 - \bar{p}_3)dt \\
=\ & \frac{\beta_3}{\theta_3}\int_0^{t_f}\Big|\theta_3(p_3 - \bar{p}_3) + a_{31}e^{mt}(p_3\bar{p}_1 - \bar{p}_3p_1) + a_{32}e^{mt}(p_3\bar{p}_2 - \bar{p}_3p_2)\Big||p_3 - \bar{p}_3|dt \\
&+ (\beta_{30} - \mu_3)\int_0^{t_f}(p_3 - \bar{p}_3)^2dt + \eta\int_0^{t_f}(p_2 - \bar{p}_2)(p_3 - \bar{p}_3)dt \\
&+ s\int_0^{t_f}(up_2 - \bar{u}\bar{p}_2)(p_3 - \bar{p}_3)dt - \int_0^{t_f}(vp_3 - \bar{v}\bar{p}_3)(p_3 - \bar{p}_3)dt \\
\leqslant\ & \frac{\beta_3}{\theta_3}\int_0^{t_f}\Big(\theta_3|p_3 - \bar{p}_3| + a_{31}e^{mt}|p_3\bar{p}_1 - \bar{p}_3p_1| + a_{32}e^{mt}|p_3\bar{p}_2 - \bar{p}_3p_2|\Big)|p_3 - \bar{p}_3|dt \\
&+ (\beta_{30} - \mu_3)\int_0^{t_f}(p_3 - \bar{p}_3)^2dt + \eta\int_0^{t_f}(p_2 - \bar{p}_2)(p_3 - \bar{p}_3)dt \\
&+ s\int_0^{t_f}(up_2 - \bar{u}\bar{p}_2)(p_3 - \bar{p}_3)dt - \int_0^{t_f}(vp_3 - \bar{v}\bar{p}_3)(p_3 - \bar{p}_3)dt \\
=\ & \frac{\beta_3}{\theta_3}\int_0^{t_f}\Big(a_{31}e^{mt}|p_3\bar{p}_1 - \bar{p}_3p_1| + a_{32}e^{mt}|p_3\bar{p}_2 - \bar{p}_3p_2|\Big)|p_3 - \bar{p}_3|dt \\
&+ (\beta_{30} - \mu_3 + \beta_3)\int_0^{t_f}(p_3 - \bar{p}_3)^2dt + \eta\int_0^{t_f}(p_2 - \bar{p}_2)(p_3 - \bar{p}_3)dt \\
&+ s\int_0^{t_f}(up_2 - \bar{u}\bar{p}_2)(p_3 - \bar{p}_3)dt - \int_0^{t_f}(vp_3 - \bar{v}\bar{p}_3)(p_3 - \bar{p}_3)dt. \qquad (4.4)
\end{aligned}$$

Now, we perform estimations to some terms of (4.4), and the other terms can be obtained by similar discussions. Applying the Cauchy inequality, there exists $M_1 > 0$ such that

$$\begin{aligned}
\int_0^{t_f}a_{31}e^{mt}|p_3\bar{p}_1 - \bar{p}_3p_1||p_3 - \bar{p}_3|dt &\leqslant a_{31}e^{mt_f}\int_0^{t_f}|(p_3\bar{p}_1 - \bar{p}_3p_1)(p_3 - \bar{p}_3)|dt \\
&= a_{31}e^{mt_f}\int_0^{t_f}|(p_3\bar{p}_1 - p_3p_1 + p_3p_1 - \bar{p}_3p_1)(p_3 - \bar{p}_3)|dt \\
&= a_{31}e^{mt_f}\int_0^{t_f}|(p_3(\bar{p}_1 - p_1)(p_3 - \bar{p}_3) + (p_3 - \bar{p}_3)p_1)(p_3 - \bar{p}_3)|dt \\
&\leqslant a_{31}e^{mt_f}\int_0^{t_f}|p_3(\bar{p}_1 - p_1)(p_3 - \bar{p}_3)| + |p_1|(p_3 - \bar{p}_3)^2dt
\end{aligned}$$

$$\leqslant \quad a_{31}e^{mt_f}M_1\int_0^{t_f}((\bar{p}_1-p_1)^2+(p_3-\bar{p}_3)^2)dt. \tag{4.5}$$

Next, since $p_i(t)$ and $\bar{p}_i(t)$ are nonnegative functions for $t\in(0,t_f)$,

$$\begin{aligned}
&\int_0^{t_f}(up_2-\bar{u}\bar{p}_2)(p_3-\bar{p}_3)dt\\
=\quad&\int_0^{t_f}(\max\Big\{0,\min\{u_{max},\frac{(q_2-sq_3)p_2}{2c}\}\Big\}p_2-\max\Big\{0,\min\{u_{max},\frac{(\bar{q}_2-s\bar{q}_3)\bar{p}_2}{2c}\}\Big\}\bar{p}_2)(p_3-\bar{p}_3)dt\\
\leqslant\quad&\int_0^{t_f}\Big|(\max\Big\{0,\min\{u_{max},\frac{(q_2-sq_3)p_2}{2c}\}\Big\}p_2-\max\Big\{0,\min\{u_{max},\frac{(\bar{q}_2-s\bar{q}_3)\bar{p}_2}{2c}\}\Big\}\bar{p}_2)(p_3-\bar{p}_3)\Big|dt\\
=\quad&\int_0^{t_f}\Big|\max\Big\{0,\min\{u_{max}p_2,\frac{(q_2-sq_3)p_2^2}{2c}\}\Big\}-\max\Big\{0,\min\{u_{max}\bar{p}_2,\frac{(\bar{q}_2-s\bar{q}_3)\bar{p}_2^2}{2c}\}\Big\}\Big||(p_3-\bar{p}_3)|dt\\
\leqslant\quad&\int_0^{t_f}\Big|\frac{(q_2-sq_3)p_2^2}{2c}-\frac{(\bar{q}_2-s\bar{q}_3)\bar{p}_2^2}{2c}\Big||p_3-\bar{p}_3|dt.
\end{aligned}$$

Moreover, since the function $f(p_2,q_2,q_3)=\dfrac{(q_2-sq_3)p_2^2}{2c}$ is locally Lipschitz, there exists $M_2>0$ so that

$$\begin{aligned}
&\int_0^{t_f}\Big|\frac{(q_2-sq_3)p_2^2}{2c}-\frac{(\bar{q}_2-s\bar{q}_3)\bar{p}_2^2}{2c}\Big||p_3-\bar{p}_3|dt\\
\leqslant\quad&M_2\int_0^{t_f}(|p_2-\bar{p}_2|+|q_2-\bar{q}_2|+|q_3-\bar{q}_3|)|p_3-\bar{p}_3|dt\\
\leqslant\quad&\frac{M_2}{2}\int_0^{t_f}((p_2-\bar{p}_2)^2+(q_2-\bar{q}_2)^2+(q_3-\bar{q}_3)^2+3(p_3-\bar{p}_3)^2)dt.
\end{aligned}$$

Hence,

$$\int_0^{t_f}(up_2-\bar{u}\bar{p}_2)(p_3-\bar{p}_3)dt\leqslant\frac{M_2}{2}\int_0^{t_f}((p_2-\bar{p}_2)^2+(q_2-\bar{q}_2)^2+(q_3-\bar{q}_3)^2+3(p_3-\bar{p}_3)^2)dt. \tag{4.6}$$

Similarly, there exists $M_3>0$ so that

$$-\int_0^{t_f}(vp_3-\bar{v}\bar{p}_3)(p_3-\bar{p}_3)dt\leqslant\frac{M_3}{2}\int_0^{t_f}((q_3-\bar{q}_3)^2+3(p_3-\bar{p}_3)^2)dt. \tag{4.7}$$

Thus, from (4.4) and (4.5)-(4.7), and note $(p_3(t_f)-\bar{p}_3(t_f))^2\geqslant 0$, there exists $L_{1,3}>0$ so that

$$m\int_0^{t_f}(p_3-\bar{p}_3)^2dt\leqslant L_{1,3}(1+e^{mt_f})\int_0^{t_f}\left(\sum_{j=1}^{3}((\bar{p}_j-p_j)^2+(\bar{q}_j-q_j)^2)\right)dt,$$

which gives an inequality of form (3.65).

Applying the analogous scheme, we obtain for $L_{2,3}>0$ so that

$$m\int_0^{t_f}(q_3-\bar{q}_3)^2dt\leqslant L_{2,3}(1+e^{mt_f}+e^{2mt_f}+e^{3mt_f})\int_0^{t_f}\left(\sum_{j=1}^{3}((\bar{p}_j-p_j)^2+(\bar{q}_j-q_j)^2)\right)dt,$$

which gives an inequality of form (3.66).

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