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Modeling and Analysis of a Nonlinear Age-Structured Model for Tumor Cell Populations with Quiescence

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Abstract We present a nonlinear first-order hyperbolic partial differential equation model to describe age-structured tumor cell populations with proliferating and quiescent phases at the avascular stage in vitro. The division rate of the proliferating cells is assumed to be nonlinear due to the limitation of the nutrient and space. The model includes a proportion of newborn cells that enter directly the quiescent phase with age zero. This proportion can reflect the effect of treatment by drugs such as erlotinib. The existence and uniqueness of solutions are established. The local and global stabilities of the trivial steady state are investigated. The existence and local stability of the positive steady state are also analyzed. Numerical simulations are performed to verify the

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results and to examine the impacts of parameters on the nonlinear dynamics of the model.

Keywords Cell cycle · Age-structured model · Proliferating and quiescent stages · Steady state · Stability

Mathematics Subject Classification 35L40 · 35B35 · 92C37

1 Introduction

The growth and invasion of tumor cells have drawn great attention of many researchers and have been studied extensively for several decades. Theoretical analysis to tumor experiments in vivo or in vitro, as one crucial approach to tumor study, is usually adopted to investigate the in-depth dynamical features at three levels: molecular, cellular and tissue, either separately or comprehensively (Bertalanffy 1957; Laird 1964; Gyllenberg and Webb 1989; Florian et al. 2005; Ayati et al. 2006; Liu et al. 2012; Bi et al. 2014). For instance, Florian et al. (2005) established a four-state (first gap G_1, synthesis stage S, second gap G_2 and mitosis stage M) cell-cycle model with explicit G_1 phase representation. They analyzed the transfer rates between G_0 (quiescent phase) and G_1 phases from the molecular level. Moreover, they revealed from the tissue level that perturbations to the transfer rates alter significantly untreated tumor growth predictions in open-loop situation but does not carry over to closed-loop simulations. Ayati et al. (2006) proposed multi-scale models of cancer tumor invasion with components at molecular level (diffusion and taxis processes), cellular level (cell age variable) and tissue level (spatial variable). The models and methods presented in Ayati et al. (2006) provide a template to develop and treat increasingly complex, mechanistic models of tumor invasion that will be more predictive and less phenomenological.

According to different growth rates and different dispersal circumstances, tumor development is classified into three distinct stages: avascular, vascular and metastatic. Tumor cells at the avascular stage grow exponentially due to the fact that all cells are nourished adequately, but retard to a linear growth phase due to a developing region of quiescent cells and necrosis in the core (Congar and Ziskin 1983). Following the linear phase, growth retards ultimately reaching a saturation level at which it apparently ceases (Folkman and Hochberg 1973; Carlsson 1977). Ward and King (1997) proposed a mathematical model for the growth of avascular tumors and studied in detail the first two stages of growth, namely the initial (exponential) and the intermediate (linear) phases. Successively, they extended the model by employing physical mechanisms which can result in growth saturation and studied the traveling waves and steady states of the model (Ward and King 1999). Recently, Alzahrani et al. (2014) extended the Gyllenberg and Webb model (Gyllenberg and Webb 1989) to a three-compartment form by keeping track of the dead cells remaining in the avascular tumor. They analyzed the variation of the densities of proliferating and quiescent cells with the quiescent cell death rate and the variation of them with the dead cell removal rate, respectively. Alzahrani and Kuang (2016) further improved the above model by considering a resource limitation form. They identified general and explicit expressions of the tumor

final size, studied the steady states of the tumor and revealed that the tumor size at the positive steady state is a strictly deceasing function of the dead cell removal rate.

However, once the tumor acquires its own blood system by the process of angiogenesis, i.e., entering the vascular stage, it will be well supplied with nutrients, increase rapidly in size and even invade the surrounding tissues (Folkman and Cotran 1976). Based on an important assumption that the blood vessels in the tumor would collapse if the pressure that exerted on the vessels by the tumor cells exceeds a critical value, Orme and Chaplain (1996) put forward a simple mathematical model to discuss the growth and invasion of the vascular tumor. They indicated that diffusion only cannot account for all observed behaviors, and hence, the growth of tumors is accompanied by the invasion of surrounding tissues. Applying the same hypothesis, Breward et al. (2004) provided a multi-phase model consisted of the volume fractions of tumor cells, extracellular material and blood vessels by using conservation of mass and momentum equations to describe and analyze the vascular tumor growth. Involving normal cells, Hubbard and Byrne (2013) presented a four-phase and multi-dimensional continuum model of vascular tumor growth. They examined the sensitivity of the model to parameter changes, captured the geometrically complex tumor boundaries and indicated that the model supports linear tumor growth rates. For more comprehensive coverage of the literature describing the mathematical and computational modeling of vascular tumor growth, we refer to the excellent reviews of Araujo and McElwain (2004) and Lowengrub et al. (2010).

Additionally, when tumor cells move by direct contacts with new organ sites or breakaway from the primary tumor through the vasculature to other parts of the body where, if conditions are favorable, the tumor cells may establish themselves as secondary tumors and tumor metastases occur (Folkman 2002). Malignant tumor cell metastasis is fatal. It is very difficult to model these processes and conduct clinical treatment. Hartung et al. (2014) constructed a transport equation model with a boundary condition for metastatic emissions to describe the metastatic spread and to estimate the risk of metastasis. Moreover, they compared the model predictions with experimental results from orthotopic breast tumor xenograft experiments conducted in Nod/Scid γ mice. Pinho et al. (2002) proposed a model of cancer treatment by chemotherapy where metastasis of the cancer cells occurs and analyzed the dynamical behaviors such as the existence and stability of equilibria theoretically and numerically. Many other mathematical models describing cancer metastases can be found in Tan (1989), Newton et al. (2013), Ramis-Conde et al. (2008) and Liotta et al. (1976).

There is always a rapid growth period at either the avascular stage or the vascular stage. At this time, tumor cells will grow exponentially because of abundant nutrients. When cell cycle is considered and cell size or age is involved, the population of dividing cells with initial synchrony in the cell cycle may lose their initial information after a few generations. However, the population continues to grow exponentially and as it does population structure reorganizes so that proportions of the population with respect to structure converge to constant values independent of the initial data. This sort of behavior is called *asynchronous exponential growth*. Mathematical models that describe this phenomenon fall within the subject of linear structured population dynamics and have been extensively developed by many researchers such as Gyllenberg and Webb (1987), Arino and Kimmel (1987), Gyllenberg and Webb (1992),

Arino et al. (1997), Dyson et al. (2002) and Brikci et al. (2008). Especially, Gyllenberg and Webb (1992) indicated that almost all of the linear age-structured cell population models as well as age-structured human population models exhibit the phenomenon of asynchronous exponential growth. The inclusion of nonlinearities in these models is usually designed to halt the exponential growth and force convergence to stable equilibria or stable cycles. Considering the competition between proliferating cells and quiescent cells, a nonlinear age-structured cell population model was studied theoretically and numerically by Akimenko and Anguelov (2016). They obtained three different regimes of population dynamics for asymptotically stable steady states of the system in numerical experiments for different initial population densities. Moreover, they studied the quasiperiodical traveling wave solutions numerically with different values of time delays and with oscillating death rate and birth modulus.

In this paper, we propose a nonlinear age-structured tumor cell population model and study its dynamical behaviors including the existence and stability of the trivial steady state and the positive steady state. Comparing with the existing age-structured cell population models that include proliferating and quiescent phases, the present model has the following generalizations.

(i) Modification of the linear age-structured model to a nonlinear case by considering the nutrient and space limitation into the birth rate of the proliferating cells (Arino et al. 1997; Dyson et al. 2002; Gabriel et al. 2012).
(ii) Emphasis of the evolution speed of individuals k = cell age/time in the cell cycle (Arino et al. 1997; Dyson et al. 2002; Brikci et al. 2008; Gabriel et al. 2012; Spinelli et al. 2006).
(iii) Consideration of the situation that the newborn cells can enter the quiescence directly with a certain constant proportion (Ayati et al. 2006; Arino et al. 1997; Brikci et al. 2008).

The organization of this paper is as follows. In Sect. 2, we present the model. Section 3 covers the existence and global stability of the trivial steady state. Section 4 deals with the existence and local stability of the positive steady state. Numerical simulations are given to illustrate the results in Sect. 5. Finally, we conclude the paper with a brief discussion and provide some problems for further study.

2 The Basic Model

We construct a system of nonlinear first-order PDEs to describe the dynamics of tumor cell populations with proliferating and quiescent phases at an avascular stage in vitro condition. The division rate of the proliferating cells is assumed to be nonlinear due to the limitation of the nutrient and space. Without loss of generality, the model is valid for other situations where the limited resource is taken into consideration at vascular or metastatic stage. The model of vital dynamics is developed based on previous studies including Ayati et al. (2006), Dyson et al. (2002) and Gabriel et al. (2012) and is schematically shown in Fig. 1. Proliferating cells in phase G_1 proceed through phases S and G_2, giving "birth" at the end of the cell cycle (phase M) to new cells, which either remain in the proliferating phase or join in the quiescent phase, whereas quiescent cells neither grow nor divide but either transit to the proliferative

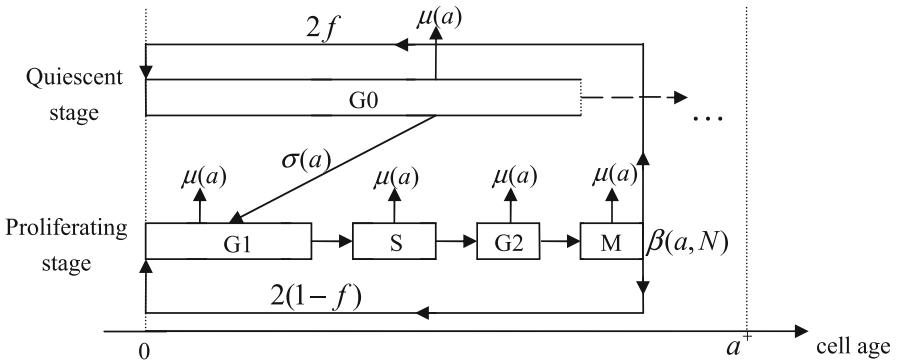


Fig. 1 The schematic of the quiescent cells in phase G_0 and proliferating cells in phases G_1 (first gap), S (synthesis), G_2 (second gap) and M (mitosis) of the cell cycle correlated with cell age

compartment or stay in phase G_0 till death and being removed from the tissue. Cell age, for both proliferating and quiescent cells, begins from the time when the cell was newly divided. For proliferating cells, cell age is relevant to the phase of the cell cycle. We assume that the evolution speed of the physiological age a with respect to time t, i.e., $\mathrm{d}a/\mathrm{d}t$, is constant and denoted by k. If, for example, $k = 0.5$, it means that the physiological age a evolves twice as slowly as real time t.

We denote $\beta(a, N(t))$ as the division rate of proliferating cells, which is related to the total number of cells N at time t. It is a decreasing function with N in a resource-limited model. We also assume that there is a proportion of newborn cells that enter quiescence with age 0 once they are divided. This proportion can reflect the dose of the treatment by drugs such as erlotinib, which has been shown in Tyson et al. (2012) that the main effect of erlotinib on cancer cells is to induce entry into quiescence (Gabriel et al. 2012). Here, we denote this fraction by f, and hence, $1 - f$ represents the part that are still remaining in the proliferating stage. We assume that there is no recruitment to the quiescent cells except the part of the new daughter cells with age 0, i.e., all the proliferating cells with age $a > 0$ will not enter the quiescent stage. However, we assume that there exists a transition rate from the quiescent stage to the proliferating stage which is caused by the fluctuation of the resource supply at some intermittent period. This rate is denoted by $\sigma(a)$ at age a.

Let $\mu(a)$ be the death rate. Define

$$S(a) := \exp\left(-\int_0^a \mu(s)\mathrm{d}s\right)$$

as the survival rate of a cell (Inaba 2006). Let a_m be the maximum survival age of a cell, then we have $S(a_m) = 0$. Hence, the assumption that $\mu(\cdot) \in L^1_{+,loc}([0, a_m))$ and $\int_0^{a_m} \mu(s)ds = \infty$ is needed. This assumption implies that for any given survival rate $\varepsilon > 0$ small enough, there exists $\varepsilon_0 > 0$ such that $S(a_m - \varepsilon_0) < \varepsilon$ holds. Set $a^+ = a_m - \varepsilon_0$. Then, we have $S(a) \leqslant S(a^+) < \varepsilon$ for all $a \in (a^+, a_m)$. Since any cell with age $a \in (a^+, a_m)$ has a sufficient small survival rate and will die as age increases no lager than ε_0, biologically, we can omit such cells and only consider the

cells whose ages lie in interval $[0, a^+]$. Let $P(t,a)$ and $Q(t,a)$ represent the densities of cells in the proliferating and quiescent stages at time t with age a, respectively. Then, our model takes the following form:

$$\begin{cases} \dfrac{\partial P}{\partial t} + k\dfrac{\partial P}{\partial a} = -\mu(a)P(t,a) - \beta(a,N(t))P(t,a) + \sigma(a)Q(t,a), \\ \dfrac{\partial Q}{\partial t} + k\dfrac{\partial Q}{\partial a} = -\mu(a)Q(t,a) - \sigma(a)Q(t,a) \end{cases} \tag{2.1}$$

with boundary conditions

$$\begin{aligned} P(t,0) &= 2(1-f)\int_0^{a^+} \beta(a,N(t))P(t,a)\mathrm{d}a, \\ Q(t,0) &= 2f\int_0^{a^+} \beta(a,N(t))P(t,a)\mathrm{d}a \end{aligned} \tag{2.2}$$

and initial conditions

$$P(0,a) = P_0(a),\ \ Q(0,a) = Q_0(a). \tag{2.3}$$

Now, we define the number of proliferating cells at time t with age between a_1 and a_2 by $\int_{a_1}^{a_2} P(t,a)\mathrm{d}a$; then, the total numbers of proliferating and quiescent cells at time t are $P(t) = \int_0^{a^+} P(t,a)\mathrm{d}a$ and $Q(t) = \int_0^{a^+} Q(t,a)\mathrm{d}a$. $N(t) = P(t) + Q(t)$ is the total number cells including proliferating ones and quiescent ones.

Throughout the paper, we always assume that:

(H_1) The death rate $\mu(\cdot)$, the dividing rate $\beta(\cdot, N)$ and the transition rate $\sigma(\cdot)$ are all nonnegative and belong to $L^\infty[0, a^+]$, where N is any nonnegative real number.

Assumption (H_1) aims to guarantee the existence and uniqueness of solutions of the system. The assumption on the non-negativity of the age-specific parameters μ, β and σ is natural. It is easy to know that μ, β and σ are all integrable on $[0, a^+]$ since they belong to $L^\infty[0, a^+]$. The assumption that β is essentially bounded means that not all cells will divide before reaching the nearly maximum survival age a^+. Such cells will die soon and the number of them can be ignored. Usually, assumptions on the death rate μ are $\mu(\cdot) \in L^1_{+,loc}([0, a_m))$ and $\int_0^{a_m} \mu(s)ds = \infty$. But we cannot deduce the essential boundedness of μ when $a \in [0, a_m)$ from these assumptions. Consequently, we replace a_m by $a^+ = a_m - \varepsilon_0$ and assume that μ is essentially bounded on $[0, a^+]$, which naturally implies that μ is locally integrable on such an interval.

In the following, we study the existences and stabilities of steady states of system (2.1)–(2.3). The existence and uniqueness of solutions of the system are proved briefly at the end of the paper (Appendix A). Similar explanations can also be referred to Inaba (1988), Inaba (2006) and Cherif et al. (2017).

3 Existence and Stability of the Trivial Steady State

The study of the trivial steady state to the tumor cell population model is meaningful since it illustrates whether the tumor cells go extinct in the long term. In this section, we will study the local and global stabilities of the trivial steady state.

Let $\bar{E}(a) := (\bar{P}(a), \bar{Q}(a))$ be a steady state of the system. Then, it must satisfy the following time-independent system of ordinary differential equations:

$$\begin{cases} \dfrac{\mathrm{d}\bar{P}}{\mathrm{d}a} = -\bar{\mu}(a)\bar{P}(a) - \bar{\beta}(a,N)\bar{P}(a) + \bar{\sigma}(a)\bar{Q}(a), \\ \dfrac{\mathrm{d}\bar{Q}}{\mathrm{d}a} = -\bar{\mu}(a)\bar{Q}(a) - \bar{\sigma}(a)\bar{Q}(a), \\ \bar{P}(0) = 2k(1-f)\displaystyle\int_0^{a^+} \bar{\beta}(a,N)\bar{P}(a)\mathrm{d}a, \quad \bar{Q}(0) = 2kf\int_0^{a^+} \bar{\beta}(a,N)\bar{P}(a)\mathrm{d}a, \end{cases} \tag{3.1}$$

where

$$\bar{\mu}(a) = \frac{\mu(a)}{k},\ \bar{\sigma}(a) = \frac{\sigma(a)}{k},\ \bar{\beta}(a,N) = \frac{\beta(a,N)}{k} \tag{3.2}$$

and $N = \int_0^{a^+}(\bar{P}(a) + \bar{Q}(a))da$. In this case, it is important to note that both N and the "birth rates" $\bar{P}(0)$ and $\bar{Q}(0)$ are constants. Let

$$\begin{aligned} \ell_1(a) &= \exp\left(-\int_0^a \bar{\mu}(\xi)\mathrm{d}\xi\right), \\ \ell_2(a,N) &= \exp\Big(-\int_0^a \bar{\beta}(\xi,N)\mathrm{d}\xi\Big), \\ \ell_3(a) &= \exp\Big(-\int_0^a \bar{\sigma}(\xi)\mathrm{d}\xi\Big). \end{aligned}$$

Obviously, the trivial steady state $\bar{E}_0 := (0,0)$ always exists and there is no boundary steady states. In fact, since $f \in (0,1)$, it follows from system (3.1) that $\bar{P}(a) = 0 \Leftrightarrow \bar{P}(0) = 0 \Leftrightarrow \bar{Q}(0) = 0 \Leftrightarrow \bar{Q}(a) = 0$ for all $a \in [0, a^+]$.

Firstly, we investigate the local stability of the trivial steady state $\bar{E}_0 := (0,0)$. To do this, we assume that

(H_2) $\beta(a,N)$ is differentiable with respect to N.

We have the following result.

Theorem 3.1 *Let assumptions* (H_1) *and* (H_2) *be satisfied. In addition, if*

$$2\int_0^{a^+} \beta(a)\ell_1(a)\ell_2(a)\left(1 - f + f\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi)d\xi\right)da < 1, \tag{3.3}$$

then the trivial steady state $\bar{E}_0 := (0,0)$ *is locally asymptotically stable, where* $\beta(a) = \beta(a,N)|_{N=0}$ *and* $\ell_2(a) = \ell_2(a,N)|_{N=0}$.

Proof Based on assumption (H_2), it is easy to calculate that the linearized system of (2.1)–(2.2) with respect to the steady state $\bar{E}_0$ is

$$\begin{cases} \dfrac{\partial x}{\partial t} + k\dfrac{\partial x}{\partial a} = -(\mu(a) + \beta(a))x(t,a) + \sigma(a)y(t,a), \\ \dfrac{\partial y}{\partial t} + k\dfrac{\partial y}{\partial a} = -\mu(a)y(t,a) - \sigma(a)y(t,a), \\ x(t,0) = 2(1-f)\displaystyle\int_0^{a^+} \beta(a)x(t,a)\mathrm{d}a, \\ y(t,0) = \dfrac{f}{1-f}x(t,0). \end{cases} \tag{3.4}$$

Separating variables as

$$x(t,a) = \mathrm{e}^{\lambda t}\bar{x}(a), \quad y(t,a) = \mathrm{e}^{\lambda t}\bar{y}(a), \tag{3.5}$$

we have

$$\begin{cases} \dfrac{\mathrm{d}\bar{x}(a)}{\mathrm{d}a} = -\bar{\lambda}\bar{x}(a) - (\bar{\mu}(a) + \bar{\beta}(a))\bar{x}(a) + \bar{\sigma}(a)\bar{y}(a), \\ \dfrac{\mathrm{d}\bar{y}(a)}{\mathrm{d}a} = -\bar{\lambda}\bar{y}(a) - \bar{\mu}(a)\bar{y}(a) - \bar{\sigma}(a)\bar{y}(a), \\ \bar{x}(0) = 2k(1-f)\displaystyle\int_0^{a^+} \bar{\beta}(a)\bar{x}(a)\mathrm{d}a, \\ \bar{y}(0) = \dfrac{f}{1-f}\bar{x}(0). \end{cases} \tag{3.6}$$

Solving the first equation of (3.6) and substituting it into $\bar{x}(0)$, we obtain that

$$\begin{aligned} \bar{x}(0) = 2k(1-f)\int_0^{a^+} \bar{\beta}(a)\bar{x}(0)\mathrm{e}^{-\bar{\lambda}a}\ell_1(a)\ell_2(a) \\ \left(1 + \frac{f}{1-f}\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi)d\xi\right)\mathrm{d}a. \end{aligned} \tag{3.7}$$

Since $\bar{x}(0) \neq 0$ ($\bar{x}(0) = 0$ leads to the trivial steady state), (3.7) yields the following characteristic equation:

$$1 = 2k\int_0^{a^+} \mathrm{e}^{-\bar{\lambda}a}\bar{\beta}(a)\ell_1(a)\ell_2(a)\left(1 - f + f\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi)d\xi\right)\mathrm{d}a. \tag{3.8}$$

Denote the right hand of (3.8) by $H(\bar{\lambda})$, and it is easy to know that $H(\bar{\lambda})$ is a continuously decreasing function with $\lim_{Re(\bar{\lambda})\to+\infty} H(\bar{\lambda}) = 0$. Hence, Eq. (3.8) has a unique real root $\bar{\lambda}^*$. Moreover, from condition (3.3) we have

$$H(0) = 2k\int_0^{a^+} \bar{\beta}(a)\ell_1(a)\ell_2(a)\left(1 - f + f\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi)d\xi\right)\mathrm{d}a < 1.$$

Thus, $\bar{\lambda}^* < 0$. Let $\bar{\lambda} = c + di$ be an arbitrary complex root to Eq. (3.8). Then,

$$1 = H(\bar{\lambda}) \leqslant |H(c + di)| \leqslant H(c),$$

which implies that $\bar{\lambda}^* > c$. Thus, all the roots of Eq. (3.8) have negative real parts.

Finally, under condition (3.3), the trivial steady state $\bar{E}_0$ is locally asymptotic stable. The proof is completed. □

In the following, we discuss the global stability of the trivial steady state. First we make the following assumption.

(H_3) The division rate $\beta(a, N(t))$ has the special form $\beta(a, N(t)) = \beta(a)\Psi(N(t))$. Moreover, $\Psi(x)$ is continuous, differentiable and strictly decreasing in $x \in [0, +\infty)$. $\Psi(0) = 1$, $\lim_{x\to+\infty} \Psi(x) = 0$.

Based on assumption (H_3), we have the following result.

Theorem 3.2 *Let assumptions* (H_1) *and* (H_3) *be satisfied. In addition, if*

$$2\int_0^{a^+} \beta(a)\ell_1(a)da < 1, \tag{3.9}$$

then the trivial steady state $\bar{E}_0 := (0, 0)$ *is globally asymptotically stable.*

Proof Denote by $N(t, a) = P(t, a) + Q(t, a)$ the total number of cells at time t with age a; then from system (2.1)–(2.3), we have:

$$\begin{cases} \dfrac{\partial N}{\partial t} + k\dfrac{\partial N}{\partial a} = -\mu(a)N(t, a) - \beta(a, N(t))P(t, a), \\ N(t, 0) = 2\displaystyle\int_0^{a^+} \beta(a, N(t))P(t, a)da, \quad N(0, a) = N_0(a). \end{cases} \tag{3.10}$$

Consider the Cauchy problem of system (3.10) on the Banach space $\mathbf{X} := \mathbb{R} \times L^1(0, a^+)$:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} 0 \\ u(t, \cdot) \end{pmatrix} = B\begin{pmatrix} 0 \\ u(t, \cdot) \end{pmatrix} + \begin{pmatrix} 2\displaystyle\int_0^{a^+} \beta(a, N(t))P(t, a)\mathrm{d}a \\ -\beta(a, N(t))P(t, \cdot) \end{pmatrix}, \\ \begin{pmatrix} 0 \\ u(0, \cdot) \end{pmatrix} = \begin{pmatrix} 0 \\ N(0, \cdot) \end{pmatrix} \in \mathbf{X}, \end{cases} \tag{3.11}$$

where the linear operator $B : D(B) \subset \mathbf{X} \to \mathbf{X}$ is defined by

$$B\begin{pmatrix} 0 \\ \phi \end{pmatrix} := \begin{pmatrix} -\phi(0) \\ -k\phi' - \mu(\cdot)\phi \end{pmatrix} \tag{3.12}$$

and $D(B)$ is given as $D(B) := \{0\} \times AC[0, a^+]$, where $AC[0, a^+]$ is the space of all absolutely continuous functions on $[0, a^+]$.

By the comparison principle and assumption (H_3), we deduce that

$$\hat{u}(t,\cdot) \leqslant \hat{z}(t,\cdot) \tag{3.13}$$

for all $t \geqslant 0$, where $\hat{u}(t,\cdot)$ is an integral solution of system (3.11) and $\hat{z}(t,\cdot)$ is a solution of the linear abstract equations

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} 0 \\ z(t,\cdot)\end{pmatrix} = B\begin{pmatrix} 0 \\ z(t,\cdot)\end{pmatrix} + \begin{pmatrix} 2\displaystyle\int_0^{a^+} \beta(a)z(t,a)\mathrm{d}a \\ 0 \end{pmatrix}, \\ \begin{pmatrix} 0 \\ z(0,\cdot)\end{pmatrix} = \begin{pmatrix} 0 \\ N(0,\cdot)\end{pmatrix} \in \mathbf{X}. \end{cases} \tag{3.14}$$

For linear problem (3.14), assume that

$$z(t,a) = \mathrm{e}^{\lambda t}\bar{z}(a). \tag{3.15}$$

Then, (3.14) becomes

$$\begin{cases} \dfrac{\mathrm{d}\bar{z}(a)}{\mathrm{d}a} = -\bar{\lambda}\bar{z}(a) - \bar{\mu}(a)\bar{z}(a), \\ \bar{z}(0) = 2\displaystyle\int_0^{a^+} \beta(a)\bar{z}(a)\mathrm{d}a, \end{cases} \tag{3.16}$$

where $\bar{\lambda} = \lambda/k$ and $\bar{\mu}(a)$ is defined in (3.2). Solving for $\bar{z}(a)$ and substituting it into $\bar{z}(0)$, we obtain

$$\bar{z}(0) = 2\int_0^{a^+} \beta(a)\bar{z}(0)\mathrm{e}^{-\bar{\lambda}a}\ell_1(a)\mathrm{d}a. \tag{3.17}$$

Since $\bar{z}(0) \neq 0$ ($\bar{z}(0) = 0$ corresponds to the trivial steady state), (3.17) leads to the following characteristic equation:

$$1 = 2\int_0^{a^+} \beta(a)\mathrm{e}^{-\bar{\lambda}a}\ell_1(a)\mathrm{d}a. \tag{3.18}$$

From condition (3.9), we know that all the roots of Eq. (3.18) have negative real parts.

Finally, we have

$$\begin{aligned} 0 &\leqslant \limsup_{t\to\infty} P(t,a) \leqslant \limsup_{t\to\infty} N(t,a) \\ &= \limsup_{t\to\infty} \hat{u}(t,a) \leqslant \limsup_{t\to\infty} \hat{z}(t,a) \\ &= \lim_{t\to\infty} \mathrm{e}^{\bar{\lambda}t}\bar{z}(a) = 0 \end{aligned}$$

and

$$\begin{aligned} 0 &\leqslant \limsup_{t\to\infty} Q(t,a) \leqslant \limsup_{t\to\infty} N(t,a) \\ &= \limsup_{t\to\infty} \hat{u}(t,a) \leqslant \limsup_{t\to\infty} \hat{z}(t,a) \\ &= \lim_{t\to\infty} \mathrm{e}^{\bar{\lambda}t}\bar{z}(a) = 0. \end{aligned}$$

The proof is completed. □

If assumption (H_3) is replaced by the following assumption (H_4), we will obtain a weaker condition than that in Theorem 3.2 for the global stability of the trivial steady state.

(H_4) $\beta(a, N(t)) = \beta(a)\Psi(N(t))$. $\Psi(x)$ is continuous, differentiable and strictly decreasing in $x \in [0, +\infty)$. $\Psi(0) = 1$, $\lim_{x\to+\infty} \Psi(x) = 0$. Moreover, there exists a positive constant $\hat{M}$ such that $\Psi(x)x < \hat{M}$ for all $x \in [0, +\infty)$.

Under assumption (H_4), we say that system (3.10) is *ultimately bounded*. In fact, integrating system (3.10) along the characteristic lines, we get

$$N(t,a) = \begin{cases} N(0, a-kt)\mathrm{e}^{-\int_0^t \mu(a-kt+k\tau)\mathrm{d}\tau} \\ \quad -\displaystyle\int_0^t \beta(a-kt+k\tau, N(\tau))P(\tau, a-kt+k\tau)\mathrm{e}^{-\int_\tau^t \mu(a-kt+ks)\mathrm{d}s}\mathrm{d}\tau, \ a > kt, \\ N\left(t-\dfrac{a}{k}, 0\right)\mathrm{e}^{-\frac{1}{k}\int_0^a \mu(\tau)\mathrm{d}\tau} \\ \quad -\dfrac{1}{k}\displaystyle\int_0^a \beta\left(\tau, N\left(t-\frac{a}{k}+\frac{\tau}{k}\right)\right) P\left(t-\frac{a}{k}+\frac{\tau}{k}, \tau\right)\mathrm{e}^{-\frac{1}{k}\int_\tau^a \mu(\xi)\mathrm{d}\xi}\mathrm{d}\tau, \ a < kt. \end{cases} \tag{3.19}$$

From $\beta(a, N(t)) = \beta(a)\Psi(N(t))$, we have

$$N(t,0) = 2\int_0^{a^+} \beta(a, N(t))P(t,a)\mathrm{d}a = 2\Psi(N(t))\int_0^{a^+} \beta(a)P(t,a)\mathrm{d}a. \tag{3.20}$$

Then,

$$\begin{aligned} N\left(t-\frac{a}{k}, 0\right) &= 2\Psi(N(t-\frac{a}{k}))\int_0^{a^+} \beta(\sigma)P\left(t-\frac{a}{k}, \sigma\right)\mathrm{d}\sigma \\ &\leqslant 2\hat{\beta}\Psi\left(N\left(t-\frac{a}{k}\right)\right)\int_0^{a^+} N(t-\frac{a}{k}, \sigma)\mathrm{d}\sigma. \end{aligned} \tag{3.21}$$

Hence, it follows from assumption (H_4), (3.19) and (3.21) that

$$N(t,a) \leqslant \begin{cases} N(0,a-kt)\mathrm{e}^{-\int_0^t \mu(a-kt+k\tau)\mathrm{d}\tau} \leqslant N_0(a-kt), & a > kt, \\ N\left(t-\dfrac{a}{k},0\right)\mathrm{e}^{-\frac{1}{k}\int_0^a \mu(\tau)\mathrm{d}\tau} \leqslant 2\hat{\beta}\hat{M}, & a < kt. \end{cases}$$

Finally, we have $N(t,a) \leqslant M := 2\hat{\beta}\hat{M}$ for all initial function $N_0(a) \leqslant M$.

Theorem 3.3 *Let assumptions (H_1) and (H_4) be satisfied. In addition, if*

$$2\int_0^{a^+} \beta(a)\ell_1(a)[\ell_2(a)]^{\gamma_0}\left(1-f+f\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)[\ell_2(\xi)]^{-\gamma_0}d\xi\right)da < 1, \tag{3.22}$$

then the trivial steady state $\bar{E}_0 := (0,0)$ is globally asymptotically stable, where $\gamma_0 := \Psi(M)$ and M is the ultimate upper bound of system (2.1)–(2.3).

Proof Consider the Cauchy problem of system (2.1)–(2.3) on the Banach space $\mathbf{X} := \mathbb{R}\times\mathbb{R}\times L^1(0,a^+)\times L^1(0,a^+)$:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} 0 \\ 0 \\ u_1(t,\cdot) \\ u_2(t,\cdot) \end{pmatrix} = L\begin{pmatrix} 0 \\ 0 \\ u_1(t,\cdot) \\ u_2(t,\cdot) \end{pmatrix} + \begin{pmatrix} 2(1-f)\displaystyle\int_0^{a^+} \beta(a,N(t))u_1(t,a)\mathrm{d}a \\ 2f\displaystyle\int_0^{a^+} \beta(a,N(t))u_1(t,a)\mathrm{d}a \\ -\beta(a,N(t))u_1(t,\cdot)+\sigma(a)u_2(t,\cdot) \\ -\sigma(a)u_2(t,\cdot) \end{pmatrix}, \\ (0,0,u_1(0,\cdot),u_2(0,\cdot))^{\mathrm{T}} = (0,0,P(0,\cdot),Q(0,\cdot))^{\mathrm{T}} \in \mathbf{X}, \end{cases} \tag{3.23}$$

where the linear operator $L : D(L) \subset \mathbf{X} \to \mathbf{X}$ is defined by

$$L(0,0,\phi_1,\phi_2)^{\mathrm{T}} := \left(-\phi_1(0), -\phi_2(0), -k\phi_1' - \mu(\cdot)\phi_1, -k\phi_2' - \mu(\cdot)\phi_2\right)^{\mathrm{T}} \tag{3.24}$$

and $D(L)$ is given as $D(L) := \{0\}\times\{0\}\times AC[0,a^+]\times AC[0,a^+]$.

By the comparison principle, we deduce that

$$\hat{u}_1(t,\cdot) \leqslant \hat{z}_1(t,\cdot) \quad \text{and} \quad \hat{u}_2(t,\cdot) \leqslant \hat{z}_2(t,\cdot) \tag{3.25}$$

for all $t \geqslant 0$, where $(\hat{u}_1(t,\cdot),\hat{u}_2(t,\cdot))$ is an integral solution of system (3.23) and $(\hat{z}_1(t,\cdot),\hat{z}_2(t,\cdot))$ is a solution of the linear abstract equations

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} 0 \\ 0 \\ z_1(t,\cdot) \\ z_2(t,\cdot) \end{pmatrix} = L\begin{pmatrix} 0 \\ 0 \\ z_1(t,\cdot) \\ z_2(t,\cdot) \end{pmatrix} + \begin{pmatrix} 2(1-f)\displaystyle\int_0^{a^+} \beta(a) z_1(t,a)\mathrm{d}a \\ 2f\displaystyle\int_0^{a^+} \beta(a) z_1(t,a)\mathrm{d}a \\ -\beta(a)\gamma_0 z_1(t,\cdot) + \sigma(a) z_2(t,\cdot) \\ -\sigma(a) z_2(t,\cdot) \end{pmatrix}, \\ (0,0,z_1(0,\cdot),z_2(0,\cdot))^{\mathrm{T}} = (0,0,P(0,\cdot),Q(0,\cdot))^{\mathrm{T}} \in \mathbf{X}. \end{cases} \tag{3.26}$$

Let C be a linear operator from $\{0\}\times\{0\}\times AC[0,a^+]\times AC[0,a^+]$ to $\mathbf{X}$ defined by

$$C\begin{pmatrix} 0 \\ 0 \\ \phi_1 \\ \phi_2 \end{pmatrix} := \begin{pmatrix} 2(1-f)\displaystyle\int_0^{a^+} \beta(a)\phi_1(a)\mathrm{d}a \\ 2f\displaystyle\int_0^{a^+} \beta(a)\phi_1(a)\mathrm{d}a \\ -\beta(\cdot)\gamma_0\phi_1 + \sigma(\cdot)\phi_2 \\ -\sigma(\cdot)\phi_2 \end{pmatrix}.$$

Let ω be any eigenvalue of the linear operator $L + C$. We can calculate that the dominated eigenvalue of linear equation (3.26) satisfies the characteristic equation

$$1 = 2(1-f)\int_0^{a^+} \beta(a)\mathrm{e}^{-\frac{\omega a}{k}}\ell_1(a)[\ell_2(a)]^{\gamma_0}\Big(1 + \frac{f}{1-f}\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)[\ell_2(\xi)]^{-\gamma_0}\mathrm{d}\xi\Big)\mathrm{d}a.$$

Then from condition (3.22), one obtains that $\omega < 0$. Thus, we have

$$\limsup_{t\to\infty} ||\hat{u}_1(t,\cdot)|| \leqslant \limsup_{t\to\infty} ||\hat{z}_1(t,\cdot)|| = \lim_{t\to\infty} |P(0)\mathrm{e}^{\frac{\omega t}{k}}| = 0$$

and

$$\limsup_{t\to\infty} ||\hat{u}_2(t,\cdot)|| \leqslant \limsup_{t\to\infty} ||\hat{z}_2(t,\cdot)|| = \lim_{t\to\infty} |Q(0)\mathrm{e}^{\frac{\omega t}{k}}| = 0,$$

where $P(0) := \int_0^{a^+} P(0,a)\mathrm{d}a$, $Q(0) := \int_0^{a^+} P(0,a)\mathrm{d}a$. That is,

$$\limsup_{t\to+\infty} \int_0^{a^+} P(t,a)\mathrm{d}a = 0, \quad \limsup_{t\to+\infty} \int_0^{a^+} Q(t,a)\mathrm{d}a = 0.$$

From the non-negativity of $P(t,a)$ and $Q(t,a)$, we have

$$\limsup_{t\to+\infty} P(t,a)\mathrm{d}a = 0, \quad \limsup_{t\to+\infty} Q(t,a)\mathrm{d}a = 0.$$

This completes the proof. □

4 Existence and Local Stability of the Positive Steady State

In this section, we discuss the existence and the local stability of the positive steady state for system (2.1)–(2.3).

Solving the second equation of system (3.1), we have

$$\bar{Q}(a) = \bar{Q}(0)\ell_1(a)\ell_3(a). \tag{4.1}$$

Solving the first equation of system (3.1) and substituting (4.1) into the solution, we get

$$\begin{aligned}\bar{P}(a) = {} & \bar{P}(0)\ell_1(a)\ell_2(a,N) \\ & + \bar{Q}(0)\ell_1(a)\ell_2(a,N)\int_0^a \bar{\sigma}(\eta)\ell_3(\eta)\ell_2^{-1}(\eta,N)\mathrm{d}\eta.\end{aligned} \tag{4.2}$$

It follows from (4.2) that the boundary condition $\bar{Q}(0)$ can be represented as

$$\bar{Q}(0) = \bar{Q}(0)U(N), \tag{4.3}$$

where

$$\begin{aligned}U(N) = {} & 2k\int_0^{a^+} \bar{\beta}(a,N)\ell_1(a)\ell_2(a,N)\,((1-f) \\ & + f\int_0^a \bar{\sigma}(\eta)\ell_3(\eta)\ell_2^{-1}(\eta,N)\mathrm{d}\eta\Big)\,\mathrm{d}a.\end{aligned} \tag{4.4}$$

Obviously, (4.3) has a unique nonzero solution if and only if $U(N) = 1$. Therefore, we have the following theorem.

Theorem 4.1 *Let $N > 0$ and assume that (H_1) holds. Then, a necessary and sufficient condition for the existence of the steady state with a total number of cells N is that*

$$U(N) = 1. \tag{4.5}$$

When this is the case, the steady state $\bar{E}(a) = (\bar{P}(a), \bar{Q}(a))$ corresponding to N is given by (4.2) and (4.1) with

$$\bar{Q}(0) = \frac{f}{1-f}\bar{P}(0) \tag{4.6}$$

and

$$\bar{P}(0) = N\Big(\int_0^{a+}\Big(\ell_1(a)\ell_2(a,N) + \frac{f}{1-f}\Big(\ell_1(a)\ell_2(a,N)\int_0^a \bar{\sigma}(\eta)\ell_3(\eta)\ell_2^{-1}(\eta,N)d\eta + \ell_1(a)\ell_3(a)\Big)\Big)da\Big)^{-1}. \tag{4.7}$$

Proof From system (3.1), we have (4.1), (4.2) and (4.6). Applying these results, we have

$$\begin{aligned} N &= \int_0^{a+}(\bar{P}(a)+\bar{Q}(a))\mathrm{d}a \\ &= \int_0^{a+}\Big(\bar{P}(0)\ell_1(a)\ell_2(a,N) \\ &\quad + \bar{Q}(0)\ell_1(a)\ell_2(a,N)\int_0^a \bar{\sigma}(\eta)\ell_3(\eta)\ell_2^{-1}(\eta,N)\mathrm{d}\eta + \bar{Q}(0)\ell_1(a)\ell_3(a)\Big)\mathrm{d}a \\ &= \bar{P}(0)\int_0^{a+}\Big(\ell_1(a)\ell_2(a,N) \\ &\quad + \frac{f}{1-f}(\ell_1(a)\ell_2(a,N)\int_0^a \bar{\sigma}(\eta)\ell_3(\eta)\ell_2^{-1}(\eta,N)\mathrm{d}\eta + \ell_1(a)\ell_3(a))\Big)\mathrm{d}a; \end{aligned}$$

then (4.7) holds. Thus to complete the proof, it suffices to show that, granted (4.1) and (4.2), (4.5) is equivalent to (4.3). The previous analysis of this section just illustrates that it is true. This completes the proof. □

In the following, we study the local stability of the positive steady state. We improve assumption (H_2) to

(H_5) $\beta(a,N)$ is differentiable with respect to N. Moreover, $\dfrac{\partial\beta(a,N)}{\partial N}$ is bounded on $[0,a^+]$.

Let $\bar{E}^*(a) := (\bar{P}^*(a),\bar{Q}^*(a))$ be a positive steady state of the system. Let $(x(t,a),y(t,a))$ be the perturbation from the steady state $(\bar{P}^*(a),\bar{Q}^*(a))$, i.e.,

$$x(t,a) = P(t,a) - \bar{P}^*(a), \quad y(t,a) = Q(t,a) - \bar{Q}^*(a).$$

Let $n(t) = N(t) - N^*$, where $N^* = \int_0^{a^+}(\bar{P}^*(a)+\bar{Q}^*(a))\mathrm{d}a$. Obviously, N^* depends on the steady state. Then,

$$\begin{aligned} n(t) &= \int_0^{a^+}(P(t,a)+Q(t,a))\mathrm{d}a - \int_0^{a^+}(\bar{P}^*(a)+\bar{Q}^*(a))\mathrm{d}a \\ &= \int_0^{a^+}(x(t,a)+y(t,a))\mathrm{d}a. \end{aligned}$$

A simple computation shows that $P(t,a)$ and $Q(t,a)$ obey the basic equations and boundary conditions of system (2.1) if and only if $x(t,a)$ and $y(t,a)$ satisfy

$$\begin{cases} \dfrac{\partial x}{\partial t}+k\dfrac{\partial x}{\partial a}=-(\mu(a)+\beta(a,N^*))x(t,a)+\sigma(a)y(t,a) \\ \quad -\beta_N(a,N^*)\bar{P}^*(a)n(t)-\Gamma_0(t,a), \\ \dfrac{\partial y}{\partial t}+k\dfrac{\partial y}{\partial a}=-(\mu(a)+\sigma(a))y(t,a), \\ x(t,0)=2(1-f)\displaystyle\int_0^{a^+}\beta(a,N^*)x(t,a)da+2(1-f)\delta(N^*)n(t)+\Gamma_1(t), \\ y(t,0)=2f\displaystyle\int_0^{a^+}\beta(a,N^*)x(t,a)\mathrm{d}a+2f\delta(N^*)n(t)+\Gamma_2(t), \end{cases} \tag{4.8}$$

where

$$\Gamma_0(t,a)=\beta_N(a,N^*)n(t)x(t,a)+\Lambda(a,n)(\bar{P}^*(a)+x(t,a)),$$

$$\Gamma_1(t)=2(1-f)\int_0^{a^+}\Gamma_0(t,a)\mathrm{d}a,\quad \Gamma_2(t)=2f\int_0^{a^+}\Gamma_0(t,a)\mathrm{d}a,$$

$$\delta(N^*)=\int_0^{a^+}\beta_N(a,N^*)\bar{P}^*(a)\mathrm{d}a$$

and

$$\Lambda(a,n)=\beta(a,N^*+n(t))-\beta(a,N^*)-\beta_N(a,N^*)n(t).$$

To investigate the local behavior of the system around the steady state, we neglect the "high-order" terms in (4.8) and consider the following linear system

$$\begin{cases} \dfrac{\partial x}{\partial t}+k\dfrac{\partial x}{\partial a}=-(\mu(a)+\beta(a,N^*))x(t,a)+\sigma(a)y(t,a)-\beta_N(a,N^*)\bar{P}^*(a)n(t), \\ \dfrac{\partial y}{\partial t}+k\dfrac{\partial y}{\partial a}=-(\mu(a)+\sigma(a))y(t,a), \\ x(t,0)=2(1-f)\displaystyle\int_0^{a^+}\beta(a,N^*)x(t,a)\mathrm{d}a+2(1-f)\delta(N^*)n(t), \\ y(t,0)=\dfrac{f}{1-f}x(t,0). \end{cases} \tag{4.9}$$

Under assumption (3.5), (4.9) becomes

$$\begin{cases} \dfrac{\mathrm{d}\bar{x}(a)}{\mathrm{d}a} = -\bar{\lambda}\bar{x}(a) - (\bar{\mu}(a)+\bar{\beta}(a,N^*))\bar{x}(a)+\bar{\sigma}(a)\bar{y}(a) - \bar{\beta}_N(a,N^*)\bar{P}^*(a)n^*, \\ \dfrac{\mathrm{d}\bar{y}(a)}{\mathrm{d}a} = -\bar{\lambda}\bar{y}(a) - (\bar{\mu}(a)+\bar{\sigma}(a))\bar{y}(a), \\ \bar{x}(0) = 2k(1-f)\displaystyle\int_0^{a^+} \bar{\beta}(a,N^*)\bar{x}(a)\mathrm{d}a + 2k(1-f)\bar{\delta}(N^*)n^*, \\ \bar{y}(0) = \dfrac{f}{1-f}\bar{x}(0), \end{cases} \tag{4.10}$$

where

$$\bar{\lambda} = \frac{\lambda}{k},\ \bar{\beta}(a,N^*) = \frac{\beta(a,N^*)}{k},\ \bar{\beta}_N(a,N^*) = \frac{\beta_N(a,N^*)}{k},$$

$$n^* = \int_0^{a^+} (\bar{x}(a)+\bar{y}(a))\mathrm{d}a,\ \bar{\delta}(N^*) = \int_0^{a^+} \bar{\beta}_N(a,N^*)\bar{P}(a)\mathrm{d}a = \frac{\delta(N^*)}{k}.$$

$\bar{\mu}(a)$ and $\bar{\sigma}(a)$ are defined in (3.2). Setting

$$\ell_2(a,N^*) = \exp\left(-\int_0^a \bar{\beta}(\xi,N^*)\mathrm{d}\xi\right)$$

and conducting regular calculations to system (4.10), we have

$$\bar{y}(a) = \bar{y}(0)\mathrm{e}^{-\bar{\lambda}a}\ell_1(a)\ell_3(a)$$

and

$$\begin{aligned} \bar{x}(a) &= \ell_1(a)\ell_2(a,N^*)\left(\bar{x}(0)\mathrm{e}^{-\bar{\lambda}a} + \int_0^a (\bar{\sigma}(\xi)\bar{y}(\xi)\right. \\ &\quad \left. -\bar{\beta}_N(\xi,N^*)\bar{P}^*(\xi)n^*)\mathrm{e}^{-\bar{\lambda}(a-\xi)}\ell_1^{-1}(\xi)\ell_2^{-1}(\xi,N^*)\mathrm{d}\xi\right) \\ &= \ell_1(a)\ell_2(a,N^*)\left(\bar{x}(0)\mathrm{e}^{-\bar{\lambda}a}\left(1+\frac{f}{1-f}\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi,N^*)\mathrm{d}\xi\right)\right. \\ &\quad \left. -n^*\bar{P}^*(0)\int_0^a \bar{\beta}_N(\xi,N^*)\mathrm{e}^{-\bar{\lambda}(a-\xi)}\mathrm{d}\xi\right), \end{aligned}$$

where the expression of $\bar{P}^*(a) = \bar{P}^*(0)\ell_1(a)\ell_2(a,N^*)$ was utilized. Substituting $\bar{y}(a)$ and $\bar{x}(a)$ into the expression of n^*, we get

$$n^* = \frac{\bar{x}(0)\int_0^{a^+} \mathrm{e}^{-\bar{\lambda}a}\ell_1(a)\left(\ell_2(a,N^*)+\frac{f}{1-f}\left(\ell_2(a,N^*)\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi,N^*)\mathrm{d}\xi+\ell_3(a)\right)\right)\mathrm{d}a}{1+\bar{P}^*(0)\int_0^{a^+} \ell_1(a)\ell_2(a,N^*)\int_0^a \bar{\beta}_N(\xi,N^*)\mathrm{e}^{-\bar{\lambda}(a-\xi)}\mathrm{d}\xi\,\mathrm{d}a}.$$

Then, $\bar{x}(a)$ can be written as

$$\bar{x}(a) = \bar{x}(0)\ell_1(a)\ell_2(a, N^*)\left(\mathrm{e}^{-\bar{\lambda}a}\left(1 + \frac{f}{1-f}g(a)\right) - h_{\bar{\lambda}} f_{\bar{\lambda}}(a)\right), \quad (4.11)$$

where

$$h_{\bar{\lambda}} = \frac{\bar{P}^*(0)\int_0^{a^+} \mathrm{e}^{-\bar{\lambda}a}\ell_1(a)\left(\ell_2(a, N^*) + \frac{f}{1-f}(\ell_2(a, N^*)g(a) + \ell_3(a))\right)\mathrm{d}a}{1 + \bar{P}^*(0)\int_0^{a^+} \ell_1(a)\ell_2(a, N^*) f_{\bar{\lambda}}(a)\mathrm{d}a},$$

$$g(a) = \int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi, N^*)\mathrm{d}\xi, \quad f_{\bar{\lambda}}(a) = \int_0^a \bar{\beta}_N(\xi, N^*)\mathrm{e}^{-\bar{\lambda}(a-\xi)}\mathrm{d}\xi.$$

Plugging (4.11) into the expression of $\bar{x}(0)$ and noting that

$$\bar{\delta}(N^*) = \int_0^{a^+} \bar{\beta}_N(a, N^*)\bar{P}^*(0)\ell_1(a)\ell_2(a, N^*)\mathrm{d}a,$$

we have

$$1 = \int_0^{a^+}\left(1 + \frac{f}{1-f}g(a)\right) r_1(a, N^*)\mathrm{e}^{-\bar{\lambda}a}\mathrm{d}a + h_{\bar{\lambda}}\int_0^{a^+}(r_2(a, N^*) - r_1(a, N^*) f_{\bar{\lambda}}(a))\mathrm{d}a, \quad (4.12)$$

where

$$r_1(a, N^*) = 2k(1-f)\bar{\beta}(a, N^*)\ell_1(a)\ell_2(a, N^*),$$
$$r_2(a, N^*) = 2k(1-f)\bar{\beta}_N(a, N^*)\ell_1(a)\ell_2(a, N^*).$$

Thus, a solution with form (3.5) will exist if and only if $\bar{\lambda}$ satisfies transcendental equation (4.12). If all $\bar{\lambda}$'s that satisfy (4.12) have negative real parts, then all solutions of the form (3.5) will approach to zero as t goes to infinity. Hence, we have the following result.

Theorem 4.2 *Assume that* (H_1), (H_5) *and (4.5) hold. In addition, if (4.12) has no solution* $\bar{\lambda}$ *with* $\mathrm{Re}(\bar{\lambda}) \geqslant 0$, *then the positive steady state* $\bar{E}^*(a) = (\bar{P}^*(a), \bar{Q}^*(a))$ *of system (2.1)–(2.3) is locally asymptotically stable. Otherwise, it is unstable.*

Remark 4.1 We analyzed the existence and stability of the positive steady state of nonlinear system (2.1)–(2.3) by applying the Gurtin–Maccamy method (Gurtin and Maccamy 1974) and obtained a transcendental equation (4.12) with respect to parameter $\bar{\lambda}$. According to our assumption on the solutions of the perturbation system, i.e., $x(t, a) = \mathrm{e}^{\lambda t}\bar{x}(a)$, $y(t, a) = \mathrm{e}^{\lambda t}\bar{y}(a)$, the positive steady state will be asymptotically stable if (4.12) has no solution $\bar{\lambda}$ with $\mathrm{Re}(\bar{\lambda}) \geqslant 0$. However, (4.12) has no monotonicity on $\bar{\lambda}$ and it is difficult to get some criteria mathematically. Hence, we regard it

as a condition of Theorem 4.2 like Theorem 7 in Gurtin and Maccamy (1974). But, we illustrate the existence (Figs. 7, 8, 9, 10) and stability (Fig. 11) of the positive steady state numerically in Sect. 5, which shows that the system really has locally asymptotically stable positive steady state if the coefficients of the system are taken appropriate values.

5 Numerical Simulations

In this section, we present some numerical examples to illustrate the local stability of the trivial steady state, the global stability of the trivial steady state and the existence and local stability of the positive steady state, respectively. It is worth noting that we numerically analyze in detail the effects of three key parameters: the evolution speed k, the proportion f of newborn cells that enter quiescence with age 0, and the death rate μ, on the cell populations. In all examples, we take the nearly maximum survival age of cells as $a^+ = 72$ hours and the transition rate $\sigma(a) = 0.02$ (Spinelli et al. 2006). Assume that the cell division rate has the form $\beta(a, N) = \beta(a)\Psi(N)$. Take

$$\beta(a) = \begin{cases} 0, & a \leqslant \bar{a}, \\ \dfrac{1}{\varrho}\dfrac{(a-\bar{a})^2}{2\varrho^2 + 2\varrho(a-\bar{a}) + (a-\bar{a})^2}, & a > \bar{a} \end{cases}$$

(see Gabriel et al. 2012) for all $a \in [0, a^+]$ and $\Psi(N) = 10^7/(N+10^7)$ for all $N \geqslant 0$, where $\bar{a} = 50$ is the time from when the proliferating cells begin to divide, and $\varrho = 2$ is a variance constant. Take the death rate as follows

$$\mu(a) = \begin{cases} \mu, & a \leqslant \bar{a}, \\ \mu + \mu(a-\bar{a})^2, & a > \bar{a} \end{cases} \tag{5.1}$$

for all $a \in [0, a^+]$.

Firstly, we investigate the local stability of the trivial steady state $\bar{E}_0$. Take $\mu = 0.002$ (Spinelli et al. 2006) and the initial functions $P(0, a) = Q(0, a) = (a^+ - a) \times 10^5/a^+$ (Brikci et al. 2008). We study the condition of Theorem 3.1 and discuss the effects of the proportion f on the local stability of the trivial steady state under different cell evolution speeds k. Let

$$\begin{aligned} J(f) &= 2\int_0^{a^+} \beta(a)\ell_1(a)\ell_2(a)\left(1 - f + f\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)\ell_2^{-1}(\xi)\mathrm{d}\xi\right)\mathrm{d}a \\ &= (1-f)\times 2\int_0^{a^+} \beta(a)\ell_1(a)\ell_2(a)\mathrm{d}a \\ &\quad + f\times 2\int_0^{a^+} \beta(a)\ell_1(a)\int_0^a \frac{\sigma(\xi)}{k}\ell_3(\xi)\frac{\ell_2(a)}{\ell_2(\xi)}\mathrm{d}\xi\mathrm{d}a. \end{aligned}$$

From Theorem 3.1, we know that the trivial steady state $\bar{E}_0$ is locally stable if $J(f) < 1$. Figure 2a shows the exact value of f such that $J(f) = 1$ under different values of k.

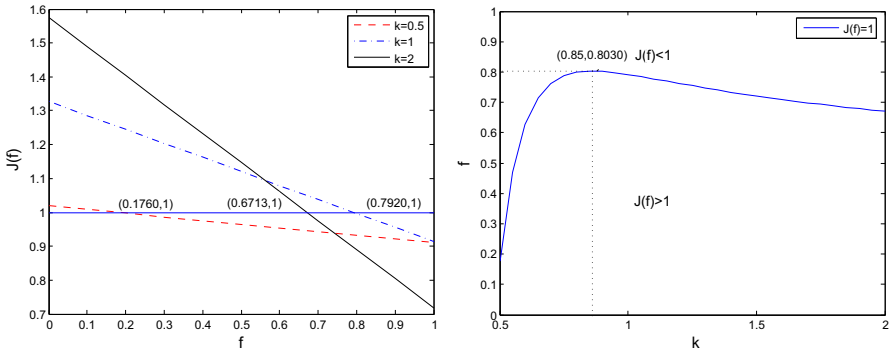


Fig. 2 **a** The effects of f on the local stability of the trivial steady state $\bar{E}_0$ when cell evolution speed k takes values 0.5, 1 and 2, respectively. **b** The effects of f on the local stability of the trivial steady state $\bar{E}_0$ as k increases. $\bar{E}_0$ is locally stable for all $J(f) < 1$

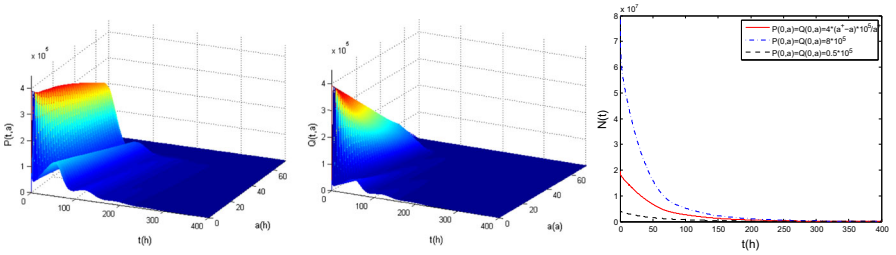


Fig. 3 **a**, **b** are the age distributions of proliferating cells $P(t, a)$ and quiescent cells $Q(t, a)$. **c** is the time series of the total number $N(t)$ under three different initial values. These three figures show the global stability of the trivial steady state $\bar{E}_0$ under conditions of Theorem 3.2

In order to cope with the condition $J(f) < 1$ in the case $k = 1$, a larger proportion f is needed than that in others cases. Figure 2b plots function $J(f) = 1$ as k increases. On one hand, it gives a curve that the tumor will go extinct when f takes values above it. On the other hand, it indicates that when cell evolution speed k is 0.85, we need the largest dose of the drug erlotinib to induce the newborn cells to enter the quiescence so that $J(f) = 1$.

Now, we illustrate the global stability of the trivial steady state $\bar{E}_0$, where we choose the initial functions as $P(0, a) = Q(0, a) = 4(a^+ - a) \times 10^5/a^+$. Take $k = 1$ and $f = 0.3$.

If we choose $\mu = 0.011$, we can calculate that

$$J(\mu) = 2\int_0^{a^+} \beta(a)\ell_1(a)\mathrm{d}a = 0.9507 < 1,$$

which satisfies condition (3.9) of Theorem 3.2. Hence, $\bar{E}_0$ is globally stable. See Fig. 3a, b. Figure 3c plots the time series of the total number N under three different

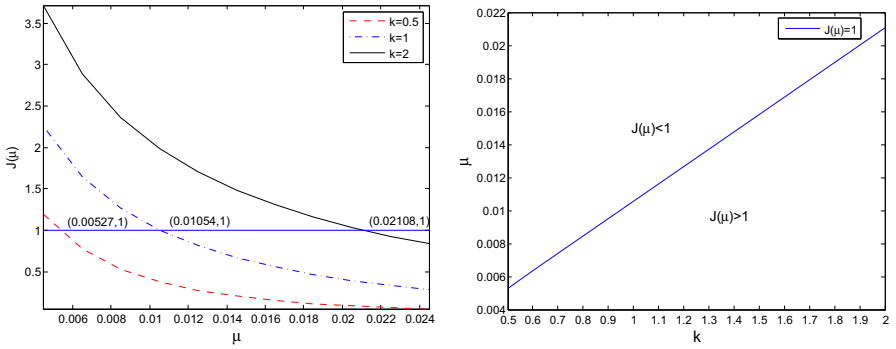


Fig. 4 **a** The effects of the death rate μ on the global stability of the trivial steady state $\bar{E}_0$ when cell evolution speed k takes values 0.5, 1 and 2, respectively. **b** The effects of the death rate μ on the global stability of the trivial steady state $\bar{E}_0$ as k increases. $\bar{E}_0$ is globally stable for all $J(\mu) < 1$

initial values, which further demonstrates the global stability of the trivial steady state $\bar{E}_0$. Note that $J(\mu)$ does not depend on the proportion f. Figure 4a plots the effects of the death rate μ on the global stability of $\bar{E}_0$ at three different cell evolution speeds $k = 0.5,\ 1$ and 2. Figure 4b plots the effects of the death rate μ on the global stability of $\bar{E}_0$ as k increases. One can see that a larger cell evolution speed needs a larger death rate to guarantee the condition $J(\mu) < 1$. Recalling the definition of $\mu(a)$ in (5.1), we have

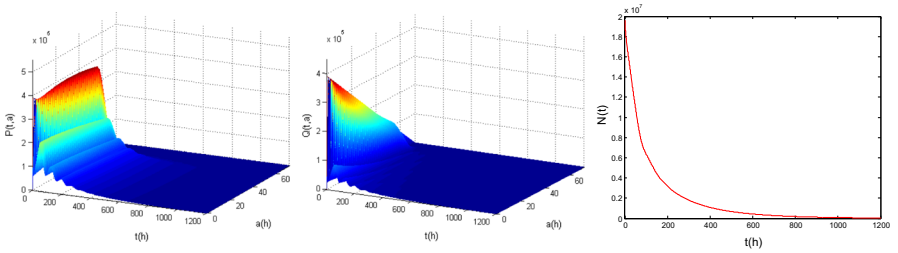
$$\begin{aligned} J(\mu) &= 2\int_0^{a^+} \beta(a)\ell_1(a)\mathrm{d}a \\ &= 2\int_0^{a^+} \beta(a)\exp\left(-\frac{\mu}{k}\left(\int_0^{\bar{a}} \mathrm{d}s + \int_{\bar{a}}^{a}(1+(s-\bar{a})^2)ds\right)\right)\mathrm{d}a. \end{aligned}$$

However, we have known from Fig. 4a that when $\mu/k = 0.01054 := \mu_0$, $J(\mu) = 1$. Hence, the death rate μ that satisfies $J(\mu) = 1$ is a linear function on the evolution speed k. Moreover, $\mu = \mu_0 k$ (Fig. 4b).

If $\mu = 0.006$, we can calculate that the maximum value of the cell number is less than 2×10^7. Take $M = 2 \times 10^7$; then, we obtain

$$\begin{aligned} \bar{J}(f) &= 2\int_0^{a^+} \beta(a)\ell_1(a)[\ell_2(a)]^{\gamma_0}\left(1 - f + f\int_0^a \bar{\sigma}(\xi)\ell_3(\xi)[\ell_2^{-1}(\xi)]^{\gamma_0}\mathrm{d}\xi\right)\mathrm{d}a \\ &= 0.9904 < 1, \end{aligned}$$

which satisfies condition (3.22). Hence, the trivial steady state $\bar{E}_0$ is globally stable as shown in Figs. 5 and 6. It is noticed that we need a death rate μ no less than 0.01054 to guarantee $J(\mu) < 1$ if $k = 1$. However, to satisfy the inequality $\bar{J}(f) < 1$ in Theorem 3.3, we only take the death rate $\mu = 0.006$. Hence, condition (3.22) is superior to condition (3.9).



(a) **(b)** **(c)**

Fig. 5 **a**, **b** are the age distributions of proliferating cells $P(t, a)$ and quiescent cells $Q(t, a)$. **c** is the time series of the total number $N(t)$. These three figures verify the global stability of the trivial steady state $\bar{E}_0$ under conditions of Theorem 3.3

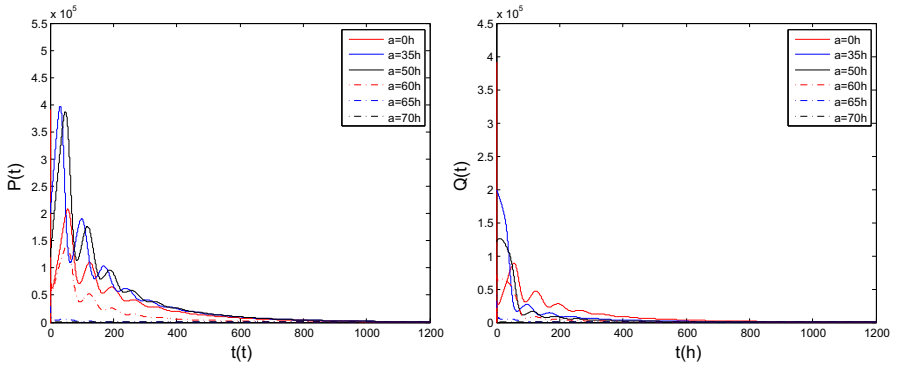


Fig. 6 The time series of $P(t, a)$ and $Q(t, a)$ at six fixed ages corresponding to Theorem 3.3

In the following, let us discuss the existence and local stability of the positive steady state. Take $\mu = 0.001$, $k = 1$ and $f = 0.3$. Based on the values of above parameters, our calculation shows that condition $U(N) = 1$ holds if the total number of cells N reaches 4.0588×10^6. The positive steady state exists. Figures 7, 8 and 9 demonstrate the existence of the positive steady state, where the initial functions are taken as $P(0, a) = Q(0, a) = (a^+ - a) \times 10^5/a^+$. Figure 7 shows the age distributions of proliferating cells P and quiescent cells Q in a long timescale. One can see that both P and Q develop steady states when time is larger than 600 hours. Figure 8 plots the trends of P and Q at six different ages and display stabilities of the two kinds of cells on some fixed ages more clearly. Figure 9 gives us a better presentation about the age distributions of P and Q at six different time points. One can see that the changes of cell's age with time are no longer distinct when $t \geqslant 300$.

It follows from (4.1) and (4.2) that steady-state system (3.1) depends continuously on the number of the newborn cells with age zero. Hence, we can say that system (2.1)–(2.3) is locally stable since the curves of newborn cells with different initial values tend to the same line (see Fig. 10). Moreover, Fig. 11 shows the stability of the total number N with respect to time t.

Figure 12a, b simulates separately the changes of cell numbers P, Q and N to the two parameters k and f at a sufficiently large time point $t_0 = 4000$ hours under the

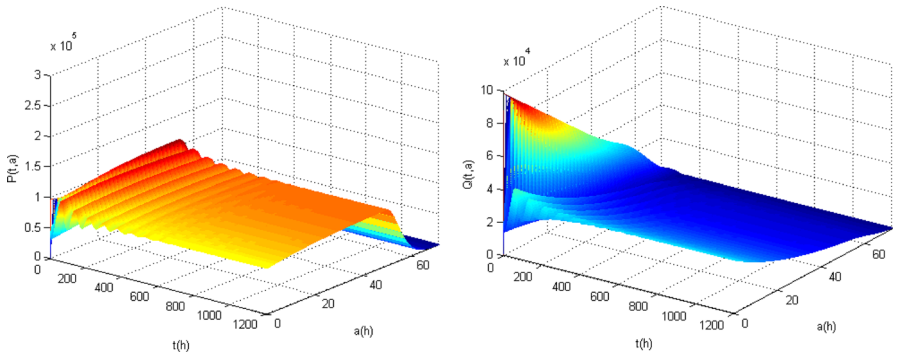


Fig. 7 The age distributions of proliferating cells $P(t, a)$ and quiescent cells $Q(t, a)$

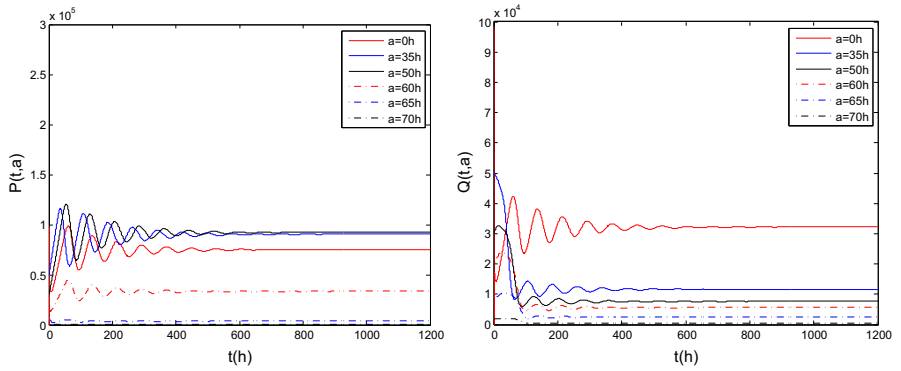


Fig. 8 The time series of $P(t, a)$ and $Q(t, a)$ at six fixed ages $a = 0$, 35, 50, 60, 65, and 70 h

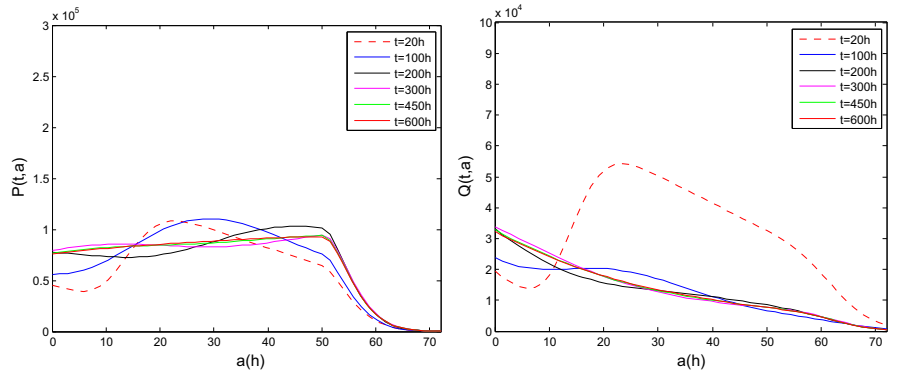


Fig. 9 The age distributions of $P(t, a)$ and $Q(t, a)$ at six different time points $t = 20$, 100, 200, 300, 450, and 600 h

same death rate $\mu = 0.001$. Figure 12a shows that the cell number of P, Q and N strictly increases with the cell evolution speed k, i.e., larger aging speed will lead to an increase in all kinds of cells. From Fig. 12b, we can observe that with the increase in

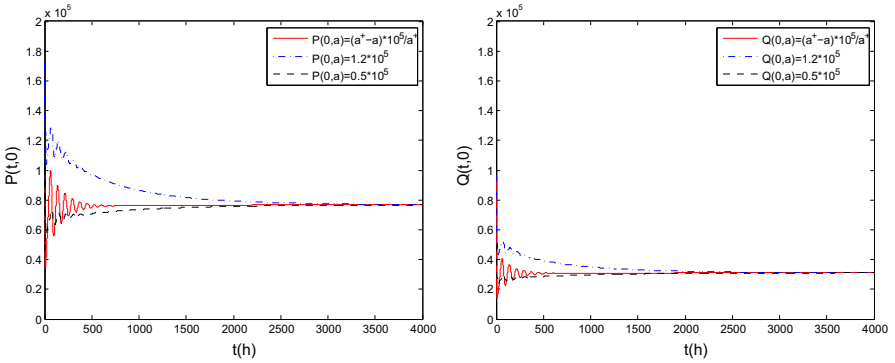


Fig. 10 The time series of $P(t, a)$ and $Q(t, a)$ with three different initial values at age $a = 0$. These two figures also illustrate the local stability of the system

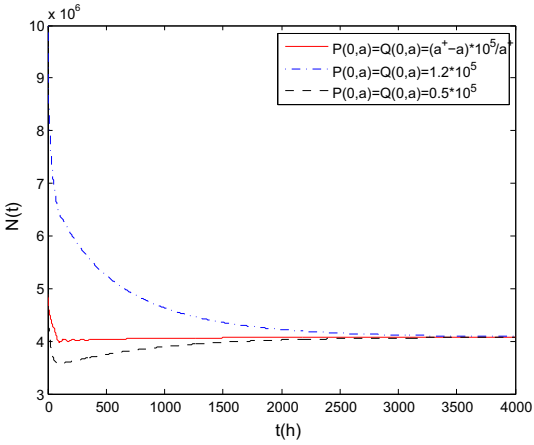


Fig. 11 The time series of the total number of cells $N(t)$ under three different initial values

the proportion f that enter the quiescence, the number of quiescent cells will increase, while the number of proliferating cells and the total cell number will decrease. One can see from Fig. 11 that to control tumor growth, we can lower the cell evolution speed or increase the dose of drug erlotinib to enlarge the proportion that enter the quiescent stage of the newborns.

6 Discussion

We proposed and analyzed a nonlinear age-structured tumor cell population model with quiescence. First, we studied the local (Theorem 3.1) and global stabilities (Theorems 3.2 and 3.3) of the trivial steady state. Then, we considered the existence (Theorem 4.1) and local stability (Theorem 4.2) of the positive steady state by applying the Gurtin–Maccamy method (Gurtin and Maccamy 1974). Finally, we performed some numerical simulations to verify the results and to examine the impacts of parameters on the asymptotic behavior of this model.

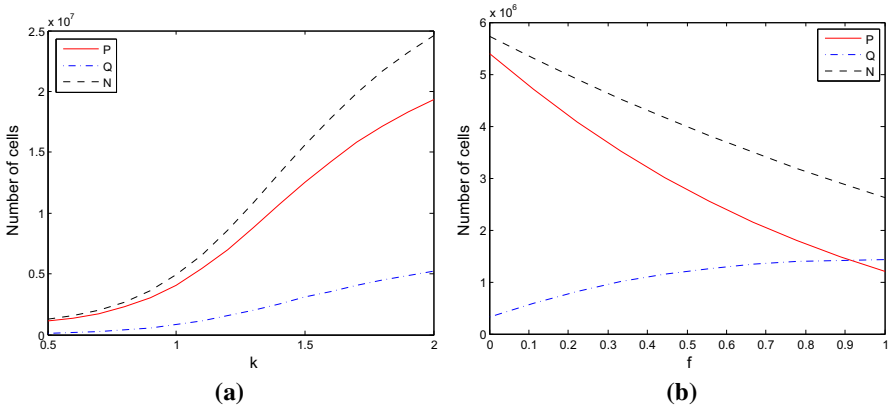


Fig. 12 **a** The trends of cell populations P, Q and N to the cell evolution speed k at an enough large time point $t_0 = 4000$ h with parameter $f = 0.3$. **b** The trends of cell populations P, Q and N to the proportion f that enter the quiescence at an enough large time point $t_0 = 4000$ h with parameter $k = 1$. Here we take $\mu = 0.001$ and the initial functions $P(0, a) = Q(0, a) = (a^+ - a) \times 10^5/a^+$ for both **a**, **b**

There are three key parameters, the evolution speed k, the proportion f of newborn cells that enter quiescence with age 0, and the death rate μ, that have been emphasized in our numerical work. For the stability of the trivial steady state, we gave an exact proportion f under which it is locally stable (see Fig. 2a), and an exact value μ under which it is globally stable (see Fig. 4a). Both of the two cases had three different k values at 0.5, 1 and 2. For the stability of the positive steady state, we illustrated that the total number of cells increases as the cell evolution speed k increases (see Fig. 12a). However, it decreases as the proportion f increases (see Fig. 12b).

Though we have given a condition to judge whether the positive steady state is stable, the criterion is not easy to be verified mathematically. However, the numerical simulation showed the fact that the population of newborn cells would tend to the same level after a long time (see Fig. 10) with three different initial functions. This implies that the age distributions of the system will approach to the same surface and then illustrate the stability of the positive steady state.

The model we presented in this paper only includes the transition from quiescent stage to proliferating stage; a natural extension is to add the transition from proliferating stage to quiescent stage in the model. However, this will raise a new challenge that the solution cannot be solved concretely, and we must search for other approaches to cope with this problem. Besides, some other developments such as detailing the four stages to the cell cycle of proliferating cells and establishing age-structured models correspondingly or considering the effects of the space and including spatial variable in the model are also very interesting and deserve further studies.

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Appendix A. Existence and Uniqueness of Solutions

Consider a Banach space $\mathbf{X} = L^1(0, a^+) \times L^1(0, a^+)$ endowed with the norm $||\phi|| = ||\phi_1|| + ||\phi_2||$ for $\phi(a) = (\phi_1(a), \phi_2(a))^T \in \mathbf{X}$, where $||\cdot||$ is the norm in L^1 and v^T is the transpose of the vector v.

Now we define a linear operator $A : D(A) \subset \mathbf{X} \to \mathbf{X}$ by

$$(A\phi)(a) := \left(-k\frac{d}{da}\phi_1(a), -k\frac{d}{da}\phi_2(a)\right)^{\mathrm{T}}. \tag{A.1}$$

The domain $D(A)$ is given as

$$D(A) = \Big\{\phi \in \mathbf{X}_+ := L^1_+(0, a^+) \times L^1_+(0, a^+) : \ \phi_1, \phi_2 \in AC[0, a^+], \\ \phi(0) = (\phi_1(0), \phi_2(0))^T\Big\},$$

where $L^1_+(0, a^+)$ denotes the positive cone of $L^1(0, a^+)$ and $AC[0, a^+]$ is the set of absolutely continuous functions on $[0, a^+)$, $\phi_1(0) = 2(1-f)\int_0^{a^+} \beta(a, N(t))\phi_1(a)\mathrm{d}a$ and $\phi_2(0) = 2f\int_0^{a^+} \beta(a, N(t))\phi_1(a)\mathrm{d}a$. We also define a nonlinear operator $F : \mathbf{X}_+ \to \mathbf{X}$ by

$$(F\phi)(a) := \begin{pmatrix} -\mu(a)\phi_1(a) - \beta(a, N)\phi_1(a) + \sigma(a)\phi_2(a) \\ -\mu(a)\phi_2(a) - \sigma(a)\phi_2(a) \end{pmatrix}. \tag{A.2}$$

Based on Assumption (H_1), it is not difficult to prove that the operator F is Lipschitz continuous and there exists a positive constant $r > 0$ such that

$$(I + rF)(\mathbf{X}_+) \subset \mathbf{X}_+, \tag{A.3}$$

where I denotes the identity operator. The proof of this result can be referred to Inaba (2006).

Set $u(t) = (P(t, \cdot), Q(t, \cdot))^T$. Then system (2.1)–(2.3) can be formulated as a nonlinear Cauchy problem on the Banach space $\mathbf{X}$:

$$\frac{\mathrm{d}u(t)}{\mathrm{d}t} = Au(t) + F(u(t)), \quad u(0) = u_0 \in \mathbf{X}, \tag{A.4}$$

where $u_0(a) = (P_0(a), Q_0(a))^{\mathrm{T}}$. We can see that operator A generates a C_0-semigroup $\{\mathrm{e}^{tA}\}_{t\geqslant 0}$ and there exist numbers $M \geqslant 1$ and $\alpha > 0$ such that

$$||\mathrm{e}^{tA}|| \leqslant M\mathrm{e}^{\alpha t}. \tag{A.5}$$

Let $r > 0$ be a constant such that (A.3) holds. Using this r and according to Busenberg et al. (1991), abstract Cauchy problem (A.4) can be rewritten as

$$\frac{\mathrm{d}u(t)}{\mathrm{d}t} = \left(A - \frac{1}{r}\right)u(t) + \frac{1}{r}(I + rF)u(t), \quad u(0) = u_0 \in \mathbf{X}. \tag{A.6}$$

Investigating problem (A.6), we obtain the mild solution by the solution of the integral equation

$$u(t) = \mathrm{e}^{-\frac{1}{r}t}\mathrm{e}^{tA}u_0 + \frac{1}{r}\int_0^t \mathrm{e}^{-\frac{1}{r}(t-s)}\mathrm{e}^{(t-s)A}(I + rF)u(s)\mathrm{d}s.$$

Let $\{S(t)\}_{t\geqslant 0}$ be the semiflow defined by the solutions of the above variation of constants formula. Then, $S(t)u_0$ can be given as the limit of the iterative sequence $\{u^n\}_{n\geqslant 0}$ such that

$$\begin{cases} u^0(t) = u_0, \\ u^{n+1}(t) = \mathrm{e}^{-\frac{1}{r}t}\mathrm{e}^{tA}u_0 + \frac{1}{r}\int_0^t \mathrm{e}^{-\frac{1}{r}(t-s)}\mathrm{e}^{(t-s)A}(I + rF)u^n(s)\mathrm{d}s. \end{cases}$$

Notice that u^{n+1} is a linear convex combination of $\mathrm{e}^{tA}u_0 \in \mathbf{X}_+$ and $\mathrm{e}^{(t-s)A}(I + rF)u^n \in \mathbf{X}_+$. Then, based on the positivity of e^{tA} and $I + rF$, we conclude that $u^{n+1} \in \mathbf{X}_+$ if $u^n \in \mathbf{X}_+$ by applying (A.3). It follows from the Lipschitz continuity of F that $\{u^n\}$ converges to the mild solution $S(t)u_0 \in \mathbf{X}_+$ uniformly. Applying (A.5), we have the estimate

$$||u(t)|| \leqslant M\mathrm{e}^{(\alpha-\frac{1}{r})t}||u_0|| + \frac{MK}{r}\int_0^t \mathrm{e}^{(\alpha-\frac{1}{r})(t-s)}||u(s)||\mathrm{d}s,$$

where $K := ||I + rF||$. From the Gronwall inequality, we can estimate that:

$$||u(t)|| \leqslant ||u_0||M\mathrm{e}^{(\alpha-\frac{1-MK}{r})t}.$$

Because the norm of the local solution grows at most exponentially as time evolves, it can be extended to a global one. Hence, the solution $S(t)u_0, t > 0$, is global.

Finally, we say that Cauchy problem (A.4) has a unique mild solution $S(t)u_0 \in \mathbf{X}_+$ for each $u_0 \in \mathbf{X}_+$, and $\mathbf{X}_+$ is positively invariant with respect to the semiflow $\{S(t)\}_{t\geqslant 0}$.

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