Modeling of tumor radiotherapy with damage and repair processes

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1 abstract

Background: Under irradiation, some cells are damaged permanently and die while some damaged cells can be self-repaired and become normal cells. The same situation happens in tumor radiotherapy. There are several models to calculate the probability of cell survival after irradiation, and several mathematical models for tumor radiotherapy which incorporate cell survival probability. However, there is no detailed studies about how both radiation damage process and cell repair process impact outcomes of tumor radiotherapy. This study focuses on impacts of these two processes in tumor radiotherapy.

Methods: The study employs mathematical modeling including mathematical analysis and numerical simulations. Based on established mathematical models for tumor growth and for irradiation, a functional reaction diffusion system for tumor radiotherapy is proposed. The model has the tumor cell population and damaged tumor cell population, and tracks their movements in the tumor site. The model considers the repair time of damaged tumor cells as a delay parameter. It is the first mathematical model to incorporate cell repair process. Detailed analysis is conducted while numerical simulations are performed with brain tumor glioma data.

Results: We obtain the functional radiation threshold which combines the tumor growth rate, the damaged cell death rate, and the damaged cell repair rate. The functional radiation threshold is a increasing function of the tumor growth rate and the damaged cell repair rate which is a decreasing function of radiation dose while the radiation damage rate is a increasing function of radiation dose. The radiation damage rate, the functional radiation threshold, and repair time roughly determine the outcomes of radiotherapy. Given radiation dose, when the radiation damage rate is greater than the functional radiation threshold, radiotherapy may destroy the tumor, or two tumor cell populations oscillate at low levels if the damaged cell repair rate is greater than the damaged tumor cell death rate and the damaged cell repair time is long enough, or Turing instability occurs if diffusion coefficients of two tumor cells are bounded each other. When the radiation damage rate is less than the functional radiation threshold, radiotherapy may control tumor growth and the tumor load decreases as the radiation dose increases if the damaged cell repair time of damaged tumor cells is less than a critical time, or two tumor cell populations oscillate at high levels if the repair time of the damaged tumor cells is beyond its

critical time.

Conclusions: The damaged tumor cell repair process increases the functional radiation threshold and complicates outcomes of radiotherapy. Our results have some medical implications or applications in precise radiotherapy. The functional radiation threshold can be computed according to particular tumor growth rate and average life time of damaged tumor cells. Based on the functional radiation threshold, appropriate radiation doses can be found under which the tumor can be destroyed or controlled. Those results may help to designed precise radiation procedures for different types of tumors in different patients.

Keywords: Radiotherapy, radiation threshold, damaged cell repair time, Hopf bifurcation, stability

2 Background

Conventional treatments for solid tumors consist of surgical resections combined with radiotherapy and chemotherapy. Radiotherapy can be applied for some tumors alone. The objective of radiotherapy is to destroy tumor cells with ionizing radiation [1–3]. Ionizing radiation consists of high-energy particles such as photons or ions, whose tracks deposit energy in cells. Ionizing particles interact with the genetic material of the cells, which disables their growth and division abilities by breaking chemical bonds. The most important radiation damage is to chromatin, that is, DNA double strand breaks. Most double strand breaks are repaired during the next one hour or so [4, 5], and a few are misrepaired. Many of the misrepairs involve a binary reaction between two different double strand breaks [6]. These lethal events are either single-hit or double-hit events in the nuclear DNA. A lethal single-hit event results from the misrepair of one or more sublethal DNA lesions created by a single particle track, whereas a lethal double-hit event results from the nonviable combination of two sublethal DNA lesions created by two radiation particle tracks [7]. Lethal single-hit and double-hit events are stochastic in nature, and are random functions of ionizing radiation dose which is measured in energy per unit mass, with 1 Gy being 1 Joule/kg [8]. However, a basic statistical data may help in understanding how radiotherapy works. One Gy dose of gamma radiation damages about 2,000 - 4,000 bases in a DNA strand, causes about 1,000 sub-lethal single-strand breaks or about 20-25 double-strand breaks [9]. DNA double-strand breaks are repaired either

by homologous recombination or nonhomologous end-joining [10]. One misrepair is enough to kill the cell at the next mitosis, and other kinds of lethal damages which are not subject to repair, e.g. lethal point mutations, are also can kill the cell. Therefore, one cell killing is defined as one unrepairable or one misrepaired double-strand break in a cell. The number of cells that are killed after ionizing radiation depends on the dose rate [7, 11]. Figure 1, the left panel explains cell DNA damage and repair processes in radiation.

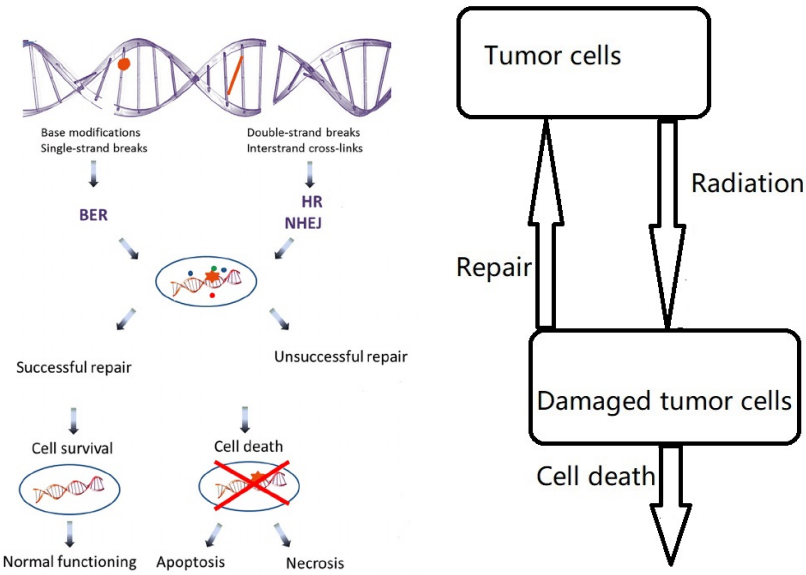

Figure 1: Left Panel shows cell DNA damage and repair processes in radiation; Right panel shows compartments of the mathematical model.

In the literature, there are several mathematical models to calculate the probability of cell survival or death after irradiation. Lea's target theory is a early model [12]. The linear quadratic (LQ) model has been widely used, which expresses the survival probability as a negative exponential of radiation dose and cell-specific radiosensitivity parameters. A comprehensive description of the linear quadratic model including control probability models [13] and their several extensions can be found in a recent review [14].

There are several mathematical models of tumor growth that incorporate radiotherapy to study effects of irradiation. These models can be classified into two groups, one compartment models and two compartment models. One compartment models consider the influence of irradiation mainly on one population of tumor cells.

Two compartment models divide tumor cells into two or more sub-populations and the influence of irradiation is on at least two sub-populations. In order to introduce our two compartment model, we give a brief review of mathematical models in the field. Along the line of one compartment models, we highlight a few of them. Enderling et al proposed a tumor growth model of three partial differential equations (PDEs) for tumor cells, extracellular matrix, and matrix-degrading enzymes, which included the linear quadratic model of irradiation in the equation for the tumor cells [15]. Powathil et al incorporated the IR model, an extension of the LQ model for irradiation, and a chemotherapy killing into a reaction-diffusion equation for tumor growth and conducted a simulation study for effects of radiotherapy and chemotherapy [16]. Swanson and colleagues have conducted a series of study for radiotherapy where they have applied one reaction diffusion equation to solid tumor growth and the LQ model or extensions for irradiation [17–19]. We proposed and studied a free boundary problem of PDEs with radiotherapy and chemotherapy [20]. Studies of radiotherapy can also use discrete-time dynamical systems or difference equations for tumor growth. A recent study by Chakwizira et al used difference equations for the synergistic combination of radiotherapy and immunotherapy [21]. Some hybrid multiscale mathematical models for radiotherapy have been also proposed. Ribba et al proposed a mathematical multiscale model for cancer growth and incorporated the LQ model for irradiation [22]. Chaplian and colleagues incorporated radiotherapy and chemotherapy into this multiscale model to study effects of cell-cycle regulation in the treatment [23]. Along the line of two compartment models, we mention several of them here. Leder et al proposed a discrete time dynamical system to study radiation dosing protocols, where two subpopulations of tumor cells were stem-like resistant cells and differentiated sensitive cells [24]. Watanabe et al proposed a system of two ordinary differential equations (ODEs) to study effects of single irradiation, where two subpopulations are dividing/proliferating cells and non-dividing cells [25]. A similar but PDE reaction diffusion system model was proposed by Perez-Garcia et al to study delay effects in response of gliomas to radiotherapy [26]. Denote proliferating tumor cell density at spatial point x and time t by $u(x,t)$, and damaged tumor cell density by $v(x,t)$. Then, the model in [26] is as follows.

$$\begin{cases} \frac{\partial u(x,t)}{\partial t} = d\Delta u(x,t) + \rho(1-u(x,t)-v(x,t))u(x,t), \\ \frac{\partial v(x,t)}{\partial t} = d\Delta v(x,t) - \frac{\rho}{k}(1-u(x,t)-v(x,t))v(x,t), \end{cases} \tag{2.1}$$

where d is the diffusion coefficient of tumor cells, k is the average number of mitosis

cycles that damaged cells are able to complete before they die, and $\frac{1}{\rho}$ is the tumor population doubling time.

Instead of using LQ model to simply incorporate radiation survival probability in modeling, we incorporate irradiation damage process and damaged cell repair process into mathematical models by using Lea's target theory [12]. When irradiation is given to a tumor, some tumor cells are hit and damaged. After irradiation, some damaged tumor cells are repaired and become proliferating tumor cells again. Repairing damaged cells takes time. We consider the repair time of damaged cells as a delay parameter. Based on models mentioned above, combining tumor growth models in [17–19], we propose a new functional reaction diffusion system for radiotherapy as follows:

$$\begin{cases} \frac{\partial u(x,t)}{\partial t} = d_1 \Delta u(x,t) + r u(x,t) \left(1 - \frac{u(x,t)+v(x,t)}{K}\right) - g(D)u(x,t) + \mu(D)v(x,t-\tau), \\ \frac{\partial v(x,t)}{\partial t} = d_2 \Delta v(x,t) + g(D)u(x,t) - \mu(D)v(x,t-\tau) - \eta v(x,t). \end{cases} \tag{2.2}$$

The radiation damage rate is given by Lea's target theory

$$g(D) = \prod_{l=1}^{N} [e^{-VD} \sum_{k=1}^{\infty} \frac{(VD)^k}{k!}]^l = (1 - e^{-VD})^{N(N+1)/2}.$$

In Lea's target theory [27, 28], each cell has N targets. One hit by radiation on a target will inactivate a cell. When each target is hit at least n times and all targets are hit, then the cell is considered dead. Hits are independent of each other, and the probability of occurrence follows a Poisson distribution. D represents the radiation dose, and V denotes the target volume. The damage cell repair rate $\mu(D)$ is given by

$$\mu(D) = 1 - [1 - e^{-VD} \sum_{k=0}^{n-1} \frac{(VD)^k}{k!}]^N.$$

We may also apply LQ model to obtain $\mu(D) \approx e^{-\alpha D - \beta D^2}$. In LQ model, the survival fraction is $e^{-\alpha D - \beta D^2}$ after radiation, which is approximately equal to the recovery or repair rate [14]. As we mentioned above that damaged cells can be repaired and recovered back to proliferating tumor cell population. This repair process takes some time τ, which is a delay parameter. We may assume cells which are in the repair process are not movable. The parameter η is the death rate of damaged tumor cells, or $\frac{1}{\eta}$ is the average life time of damaged tumor cells. Damaged tumor cells may have a different motility from non-damaged tumor cells. Actually, Harpold et al pointed

out that the damaged cells and resistant cells have different diffusion coefficients [29]. We denote the diffusion coefficient of tumor cells by d_1, and the diffusion coefficient of damaged tumor cells by d_2. The right panel in Figure 1 depicts our model scheme.

From the viewpoint of dynamical systems, radiotherapy is a finite-time perturbation to the system of the mathematical model for tumor growth. We conducted a general study about finite-time perturbations of dynamical systems [30]. For analysis of mathematical models for tumor radiotherapy, there are two types. One is numerical simulations with finite periods of time based on chosen models to give numerical predictions, and the other is asymptotical analysis of chosen models to provide insights for the treatments. To obtain a full spectrum of the dynamical behavior of our proposed model and deep insights on how irradiation affects tumor growth for a long period of time, it is suggested to conduct asymptotic analysis of the model. Particularly, irradiation has a delay effect, which also requires to explore its dynamics over the long run. In this study, we focus on asymptotic analysis of our model, but also perform finite-time numerical simulations with a careful parameter study about brain tumor gliomas from the literature.

From our analysis, we find the combined parameter $(1 + \frac{\mu(D)}{\eta})r$ is critical for the classification of our model dynamical behaviors. We then define a functional radiation threshold $R(D) = (1 + \frac{\mu(D)}{\eta})r$ which is a combination of the tumor growth rate r, the damaged tumor cell death rate η, and the damaged tumor cell repair rate $\mu(D)$ which is a function of radiation dose D. $R(D)$ is a increasing function of three arguments, the tumor growth rate, the average life time of damaged tumor cells, and the damage cell repair rate which is a decreasing function of radiation dose. The radiation damage rate $g(D)$ is a increasing function of radiation dose D. Combining with the repair time of damaged tumor cells, $R(D)$ serves as a critical value for the radiation damage rate $g(D)$ which roughly determines the dynamical patterns of radiotherapy. When $g(D) > R(D)$, the system has one spatially uniform steady state where both types of tumor cells disappear; at the critical repair time, the system undergoes Hopf bifurcations, and the Turing instability occurs as the ratio of two diffusion coefficients passing specific values, which also observed in [1]. When $g(D) < R(D)$, the system has a second spatially uniform steady state where both types of tumor cells exist; at a different critical repair time, the system also undergoes Hopf bifurcations. The overall medical implication of our results is that the dosage of radiation therapy may be refined according to different types of tumors and different

patients, radiotherapy may control the tumor growth and the radiation dose can reduce the total tumor load precisely while reduce harmfulness of radiotherapy.

The rest of the paper is organized as follows. In Section of methods and results, we conduct detailed analysis, and using brain tumor glioma data, we perform several numerical simulations. In Section of discussion, we give detailed medical implications of our analysis. We close our presentation with a brief conclusion section.

3 Methods and results

3.1 Analysis of the model

In this subsection, we conduct a detailed analysis for our model. The model system has two uniform steady states. We find conditions for their asymptotical stability. We obtain the conditions of the repair time for the system to have periodic solutions, also obtain the condition under which the Turing instability occurs.

Let Ω be an open set in $\mathbb{R}^3$ (or $\mathbb{R}$ or $\mathbb{R}^2$), which is considered as the tumor site. To complete our mathematical model, we give non-flux boundary condition and initial conditions which are functions. Denote the unit outward normal vector of the boundary $\partial\Omega$ by ν. Then, our complete mathematical model for radiotherapy is given as follows.

$$\begin{cases} \frac{\partial u(x,t)}{\partial t} = d_1\Delta u(x,t) + ru(x,t)\left(1 - \frac{u(x,t)+v(x,t)}{K}\right) - g(D)u(x,t) + \mu(D)v(x,t-\tau),\ x \in \Omega, \\ \frac{\partial v(x,t)}{\partial t} = d_2\Delta v(x,t) + g(D)u(x,t) - \eta v(x,t) - \mu(D)v(x,t-\tau),\ x \in \Omega,\ t > 0, \\ \frac{\partial u(x,t)}{\partial \nu} = \frac{\partial v(x,t)}{\partial \nu} = 0,\ x \in \partial\Omega, t > 0, \\ u(x,t) = u_0(x,t) \geq 0,\ v(x,t) = v_0(x,t) \geq 0,\ x \in \Omega,\ t \in [-\tau, 0]. \end{cases} \tag{3.1}$$

The system (3.1) has two spatially uniform steady states $E_0 = (0,0)$ and $E^* = (u^*, v^*)$, where

$$u^* = \frac{[r(\mu(D)+\eta) - \eta g(D)]K}{(\mu(D)+\eta+g(D))r},\ v^* = \frac{g(D)u^*}{\mu(D)+\eta} = \frac{[r(\mu(D)+\eta) - \eta g(D)]g(D)K}{(\mu(D)+\eta+g(D))(\mu(D)+\eta)r}.$$

When $g(D) < (1 + \frac{\mu(D)}{\eta})r$, E^* is a positive steady state.

3.1.1 Stability of E_0, Hopf bifurcation and Turing instability

In the following, we will study the stability of E_0. The linearization of (3.1) at E_0 is

$$\begin{cases} \frac{\partial u(x,t)}{\partial t} = d_1\Delta u(x,t) + (r - g(D))u(x,t) + \mu(D)v(x,t-\tau),\ x \in \Omega,\ t > 0, \\ \frac{\partial v(x,t)}{\partial t} = d_2\Delta v(x,t) + g(D)u(x,t) - \eta v(x,t) - \mu(D)v(x.t-\tau),\ x \in \Omega,\ t > 0, \\ \frac{\partial u(x,t)}{\partial \nu} = \frac{\partial v(x,t)}{\partial \nu} = 0,\ x \in \partial\Omega, t > 0, \\ u(x,t) = u_0(x,t) \geq 0,\ v(x,t) = v_0(x,t) \geq 0,\ x \in \Omega,\ t \in [-\tau, 0]. \end{cases} \tag{3.2}$$

The system (3.2) has a sequence of associated characteristic equations [31, 32]

$$\lambda^2 + a_{1,n}\lambda + a_{0,n} + (b_{1,n}\lambda + b_{0,n})\mathrm{e}^{-\lambda\tau} = 0,\ n \in \mathbb{N}_0, \tag{3.3}$$

where

$$\begin{aligned} a_{1,n} &= (d_1 + d_2)\kappa_n + \eta + g(D) - r, \\ a_{0,n} &= d_1 d_2 \kappa_n^2 + [\eta d_1 + (g(D) - r)d_2]\kappa_n + (g(D) - r)\eta, \\ b_{1,n} &= \mu(D), \\ b_{0,n} &= (d_1\kappa_n - r)\mu(D), \end{aligned}$$

and κ_n satisfies the eigenvalue problem

$$\begin{cases} -\Delta\varphi(x) = \kappa_n\varphi(x), x \in \Omega, \\ \frac{\partial\varphi}{\partial\nu} = 0,\ x \in \partial\Omega, \end{cases}$$

and $0 = \kappa_0 < \kappa_1 \leq \kappa_2 \leq \cdots$.

Lemma 3.1. *If $g(D) > (1 + \frac{\mu(D)}{\eta})r$, then E_0 is locally asymptotically stable when $\tau = 0$. If $g(D) < (1 + \frac{\mu(D)}{\eta})r$, then E_0 is unstable when $\tau = 0$.*

Proof. When $\tau = 0$, the characteristic equations (3.3) become

$$\lambda^2 + (a_{1,n} + b_{1,n})\lambda + a_{0,n} + b_{0,n} = 0.$$

If $g(D) > (1 + \frac{\mu(D)}{\eta})r$, we have

$$a_{1,n} + b_{1,n} = (d_1 + d_2)\kappa_n + g(D) - r + \mu(D) + \eta > 0$$

and

$$a_{0,n} + b_{0,n} = d_1 d_2 \kappa_n^2 + [(\mu(D) + \eta)d_1 + (g(D) - r)d_2]\kappa_n + g(D)\eta - (\eta + \mu(D))r > 0.$$

So all roots of (3.3) have negative real parts when $\tau = 0$. This implies that E_0 is locally asymptotically stable when $\tau = 0$.

If $g(D) < (1 + \frac{\mu(D)}{\eta})r$, we have $a_{0,0} + b_{0,0} = g(D)\eta - (\eta + \mu(D))r < 0$. So (3.3) has at least one root with positive real part. This implies that E_0 is unstable when $\tau = 0$. □

In the following, we will discuss the existence of Hopf bifurcations. Suppose (3.3) has a pair roots $\pm \mathrm{i}\omega(\omega > 0)$ for some $\tau > 0$ and $n \in \mathbb{N}_0$, we get

$$-\omega^2 + a_{1,n}\mathrm{i}\omega + a_{0,n} + (b_{1,n}\mathrm{i}\omega + b_{0,n})(\cos\omega\tau - \mathrm{i}\sin\omega\tau) = 0.$$

Separating the real and imaginary parts, we have

$$\begin{cases} \omega^2 - a_{0,n} = b_{1,n}\omega\sin\omega\tau + b_{0,n}\cos\omega\tau, \\ a_{1,n}\omega = b_{0,n}\sin\omega\tau - b_{1,n}\omega\cos\omega\tau. \end{cases} \tag{3.4}$$

Squaring each sides of the first equation above and plus, it gives

$$\omega^4 + (a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)\omega^2 + a_{0,n}^2 - b_{0,n}^2 = 0. \tag{3.5}$$

Denote $z = \omega^2$, (3.5) can be rewritten as

$$z^2 + (a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)z + a_{0,n}^2 - b_{0,n}^2 = 0. \tag{3.6}$$

(3.6) has two roots

$$z_n^{\pm} = \frac{1}{2}\left[2a_{0,n} + b_{1,n}^2 - a_{1,n}^2 \pm \sqrt{(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2)}\right].$$

If $a_{0,n}^2 - b_{0,n}^2 < 0$, (3.6) has a positive root z_n^+. If $a_{0,n}^2 - b_{0,n}^2 \geq 0$, $a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 < 0$ and $(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) \geq 0$, (3.6) has two positive roots $z_n^{\pm}$. Denote $\omega_n^{\pm} = \sqrt{z_n^{\pm}}$,

$$\mathcal{D}_1 = \{n \in \mathbb{N}_0 | a_{0,n}^2 - b_{0,n}^2 < 0\},$$

$$\mathcal{D}_2 = \{n \in \mathbb{N}_0 | a_{0,n}^2 - b_{0,n}^2 > 0,\ a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 < 0 \text{ and } (a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) > 0\},$$

$$\mathcal{D}_3 = \{n \in \mathbb{N}_0 | a_{0,n}^2 - b_{0,n}^2 > 0,\ a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 < 0 \text{ and } (a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) = 0\},$$

$$\tau_{j,n}^{\pm} = \begin{cases} \frac{1}{\omega_n^{\pm}}\left[\arccos\frac{(\omega_n^{\pm 2} - a_{0,n})b_{0,n} - a_{1,n}b_{1,n}\omega_n^{\pm 2}}{b_{0,n}^2 + b_{1,n}^2\omega_n^{\pm 2}} + 2j\pi\right], & \sin\omega_n^{\pm}\tau_{j,n}^{\pm} \geq 0, \\ \frac{1}{\omega_n^{\pm}}\left[-\arccos\frac{(\omega_n^{\pm 2} - a_{0,n})b_{0,n} - a_{1,n}b_{1,n}\omega_n^{\pm 2}}{b_{0,n}^2 + b_{1,n}^2\omega_n^{\pm 2}} + 2(j+1)\pi\right], & \sin\omega_n^{\pm}\tau_{j,n}^{\pm} < 0, \end{cases}$$

where $\sin\omega_n^{\pm}\tau_{j,n}^{\pm} = \frac{(\omega_n^{\pm 2}-a_{0,n})b_{1,n}\omega_n^{\pm}-a_{1,n}b_{0,n}\omega_n^{\pm}}{b_{0,n}^2+b_{1,n}^2\omega_n^{\pm 2}}$, $j \in \mathbb{N}_0$.

Let $\lambda_n = \alpha_n(\tau) \pm \mathrm{i}\omega_n(\tau)$ be a pair roots of (3.3) for some $n \in \mathbb{N}_0$, then we have the following conclusion.

Lemma 3.2. *For characteristic equations* (3.3)*, we have*

(i) $\alpha_n'(\tau_{n,j}^+) > 0$ *for* $n \in \mathcal{D}_1$.

(ii) $\alpha_n'(\tau_{n,j}^+) > 0$ *and* $\alpha_n'(\tau_{n,j}^-) < 0$ *for* $n \in \mathcal{D}_2$.

(iii) $\alpha_n'(\tau_{n,j}^{\pm}) = 0$ *for* $n \in \mathcal{D}_3$.

Proof. Differentiating the two sides of (3.3) with respect to τ, it follows that

$$(2\lambda + a_{1,n} + b_{1,n}\mathrm{e}^{-\lambda\tau} - \tau(b_{1,n}\lambda + b_{0,n})\mathrm{e}^{-\lambda\tau})\frac{\mathrm{d}\lambda}{\mathrm{d}\tau} - (b_{1,n}\lambda + b_{0,n})\lambda\mathrm{e}^{-\lambda\tau} = 0.$$

Thus,

$$\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right)^{-1} = \frac{(2\lambda + a_{1,n})\mathrm{e}^{\lambda\tau} + b_{1,n}}{\lambda(b_{1,n}\lambda + b_{0,n})} - \frac{\tau}{\lambda}.$$

From (3.3) and (3.4), we have

$$\begin{aligned}\mathrm{Re}\left(\tfrac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right)^{-1}|_{\tau=\tau_{j,n}^{\pm}} &= \mathrm{Re}\left[-\tfrac{2\lambda+a_{1,n}}{\lambda(\lambda^2+a_{1,n}\lambda+a_{0,n})} + \tfrac{b_{1,n}}{\lambda(b_{1,n}\lambda+b_{0,n})} - \tfrac{\tau}{\lambda}\right]|_{\tau=\tau_{j,n}^{\pm}} \\ &= \tfrac{\pm\sqrt{(a_{1,n}^2-2a_{0,n}-b_{1,n}^2)^2-4(a_{0,n}^2-b_{0,n}^2)}}{b_{0,n}^2+b_{1,n}^2\omega_n^{\pm 2}}.\end{aligned}$$

Since $\mathrm{sign}\left\{\alpha_n'(\tau_{j,n}^{\pm})\right\} = \mathrm{sign}\left\{\mathrm{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right)^{-1}|_{\tau=\tau_{j,n}^{\pm}}\right\}$, the conclusion is verified. □

Denote

$$\tau_1^* = \min_{n\in\mathcal{D}_1}\{\tau_{0,n}^+\},\ \tau_2^* = \min_{n\in\mathcal{D}_2\cup\mathcal{D}_3}\{\tau_{0,n}^{\pm}\},\ \tau^* = \min\{\tau_1^*, \tau_2^*\}.$$

From the Lemma 3.1, 3.2 and an easy argument, we have the following Lemma.

Lemma 3.3. *If* $g(D) > (1 + \frac{\mu(D)}{\eta})r$*, we have*

(i) If $a_{0,n}^2 - b_{0,n}^2 \geq 0$ *and* $a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 \geq 0$ *or* $(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) < 0$*, then all root of* (3.3) *have negative real part for* $\tau \geq 0$.

(ii) If $a_{0,n}^2 - b_{0,n}^2 < 0$ *or* $a_{0,n}^2 - b_{0,n}^2 \geq 0$*,* $a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 < 0$ *and* $(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) \geq 0$ *for some* $n \in \mathbb{N}_0$*, then then all root of* (3.3) *have negative real part for* $\tau \in [0, \tau^*)$.

Lemma 3.4. *For characteristic equations* (3.3)*, we have*

(i) If $a_{0,n}^2 - b_{0,n}^2 < 0$ *for some* $n \in \mathbb{N}_0$*, then* (3.3) *has a pair purely imaginary roots when* $\tau = \tau_{j,n}^+$*.*

(ii) If $a_{0,n}^2 - b_{0,n}^2 \geq 0$*,* $a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 < 0$ *and* $(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) \geq 0$ *for some* $n \in \mathbb{N}_0$*, then* (3.3) *has a pair purely imaginary roots when* $\tau = \tau_{j,n}^{\pm}$*.*

From Lemma 3.2, 3.3 and 3.4, we have theorems as follows.

Theorem 3.5. *Suppose* $g(D) > (1 + \frac{\mu(D)}{\eta})r$*, then*

(i) If $a_{0,n}^2 - b_{0,n}^2 \geq 0$ *and* $a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 \geq 0$ *or* $(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) < 0$*, then* E_0 *is locally asymptotically stable for* $\tau \geq 0$*.*

(ii) If $a_{0,n}^2 - b_{0,n}^2 < 0$ *or* $a_{0,n}^2 - b_{0,n}^2 \geq 0$*,* $a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2 < 0$ *and* $(a_{1,n}^2 - 2a_{0,n} - b_{1,n}^2)^2 - 4(a_{0,n}^2 - b_{0,n}^2) \geq 0$ *for some* $n \in \mathbb{N}_0$*, then* E_0 *is locally asymptotically stable for* $\tau \in [0, \tau^*)$*.*

Theorem 3.6. *The system* (3.1) *undergoes Hopf bifurcation at* E_0*, when* $\tau = \tau_{j,n}^+ (\tau = \tau_{i,n}^{\pm})$*, for* $n \in \mathcal{D}_1 (n \in \mathcal{D}_2)$ *and* $j \in \mathbb{N}_0$*.*

Now, we give some sufficient conditions to ensure that $a_{0,n}^2 - b_{0,n}^2 < 0$. Suppose $g(D) > (1 + \frac{\mu(D)}{\eta})r$, we have $a_{0,n} + b_{0,n} > 0$ for $n \in \mathbb{N}_0$. In this condition, we only need $a_{0,n} - b_{0,n} < 0$ to ensure that $a_{0,n}^2 - b_{0,n}^2 < 0$.

$$a_{0,n} - b_{0,n} = d_1 d_2 \kappa_n^2 + [(\eta - \mu(D))d_1 + (g(D) - r)d_2]\kappa_n + \eta g(D) + (\mu(D) - \eta)r.$$

Obviously, $a_{0,0} - b_{0,0} = \eta g(D) + r(\mu(D) - \eta) > 0$. If $\eta \geq \mu(D)$, then we can get $a_{0,n} - b_{0,n} > 0$ for all $n \in \mathbb{N}_0$. So we consider $\eta < \mu(D)$. To ensure that $a_{0,n} - b_{0,n} < 0$ for some $\kappa_n > 0$, we need

$$(\eta - \mu(D))d_1 + (g(D) - r)d_2 < 0$$

and

$$[(\eta - \mu(D))d_1 + (g(D) - r)d_2]^2 - 4d_1 d_2[\eta g(D) + (\mu(D) - \eta)r] > 0.$$

The last two inequalities are true if and only if $m_1 < \frac{d_1}{d_2} < m_2$ or $\frac{d_1}{d_2} > \max\{m_1, m_3\}$, where

$$\begin{aligned}
m_1 &= \tfrac{g(D)-r}{\mu(D)-\eta}, \\
m_2 &= \tfrac{g(D)+r}{\mu(D)+\eta} + \tfrac{2\eta g(D)}{(\mu(D)-\eta)^2} - \sqrt{\tfrac{4rg(D)}{(\mu(D)-\eta)^2} + \tfrac{4\eta g(D)(r+g(D))}{(\mu(D)-\eta)^3} + \tfrac{4\eta^2 g(D)^2}{(\mu(D)-\eta)^4}}, \\
m_3 &= \tfrac{g(D)+r}{\mu(D)+\eta} + \tfrac{2\eta g(D)}{(\mu(D)-\eta)^2} + \sqrt{\tfrac{4rg(D)}{(\mu(D)-\eta)^2} + \tfrac{4\eta g(D)(r+g(D))}{(\mu(D)-\eta)^3} + \tfrac{4\eta^2 g(D)^2}{(\mu(D)-\eta)^4}}.
\end{aligned}$$

$a_{0,n} - b_{0,n}$ is a quadratic polynomial about κ_n and has two roots, $\mu(D)^{\pm} =$

$$\frac{(\mu(D)-\eta)d_1 + (r-g(D))d_2 \pm \sqrt{[(\mu(D)-\eta)d_1 + (r-g(D))d_2]^2 - 4d_1d_2[\eta g(D) + (\mu(D)-\eta)r]}}{2d_1d_2}.$$

Denote

$$n_1 = \min\{n \in \mathbb{N} | \kappa_n > \mu(D)^-\} \text{ and } n_2 = \max\{n \in \mathbb{N} | \kappa_n < \mu(D)^+\}.$$

From Theorem 3.6, we have

Corollary 3.7. *If $g(D) > (1 + \frac{\mu(D)}{\eta})r$, $\mu(D) > \eta$ and $m_1 < \frac{d1}{d2} < m_2$ or $\frac{d_1}{d_2} > \max\{m_1, m_3\}$, then $a_{0,n}^2 - b_{0,n}^2 < 0$ for $n_1 \le n \le n_2$, that implies system (3.1) undergoes Hopf bifurcation at E_0 when $\tau = \tau_{j,n}^+$, for $n_1 \le n \le n_2$ and $j \in \mathbb{N}_0$.*

We claim that Turing instability may occurs. In the case where Corollary 3.7 conditions are satisfied, that is, if $a_{1,0}^2 - 2a_{0,0} - b_{1,0}^2 \ge 0$ or $(a_{1,0}^2 - 2a_{0,0} - b_{1,0}^2)^2 - 4(a_{0,0}^2 - b_{0,0}^2) < 0$, then the equilibrium E_0 of the system (3.1) without diffusion is locally asymptotically stable. We choose $\tau = \tau_{j,n}^+ + \varepsilon$, where ε is a small positive constant, then (3.3) has at least a pair roots with positive real part, so the steady state E_0 is unstable, Turing instability occurs.

Theorem 3.8. *Suppose $g(D) > (1+\frac{\mu(D)}{\eta})r$, $\mu(D) > \eta$, $m_1 < \frac{d1}{d2} < m_2$, and $\tau = \tau_{j,n}^+ + \varepsilon$ (ε is a small positive constant), then if $a_{1,0}^2 - 2a_{0,0} - b_{1,0}^2 \ge 0$ or $(a_{1,0}^2 - 2a_{0,0} - b_{1,0}^2)^2 - 4(a_{0,0}^2 - b_{0,0}^2) < 0$, E_0 is Turing unstable.*

3.1.2 Stability of E^* and Hopf bifurcation

In this subsection, we study the stability of the positive uniform steady state E^*. Because E^* exists if and only if $g(D) < (1 + \frac{\mu(D)}{\eta})r$, so we always assume $g(D) < (1 + \frac{\mu(D)}{\eta})r$ in this subsection.

Firstly, linearizing the system (3.3) at E^*, we get the corresponding characteristic equation which is

$$\lambda^2 + \tilde{a}_{1,n}\lambda + \tilde{a}_{0,n} + (\tilde{b}_{1,n}\lambda + \tilde{b}_{0,n})\mathrm{e}^{-\lambda\tau} = 0,\ n \in \mathbb{N}_0, \tag{3.7}$$

where

$$\begin{aligned}
&\tilde{a}_{1,n} = (d_1+d_2)\kappa_n + \tfrac{\mu(D)g(D)}{\mu(D)+\eta} + \tfrac{(\mu(D)+\eta)r-\eta g(D)}{\mu(D)+\eta+g(D)} + \eta,\\
&\tilde{a}_{0,n} = [d_1\kappa_n + \tfrac{\mu(D)g(D)}{\mu(D)+\eta} + \tfrac{(\mu(D)+\eta)r-\eta g(D)}{\mu(D)+\eta+g(D)}](d_2\kappa_n + \eta) + \tfrac{[(\mu(D)+\eta)r-\eta g(D)]g(D)}{\mu(D)+\eta+g(D)},\\
&\tilde{b}_{1,n} = \mu(D),\\
&\tilde{b}_{0,n} = \mu(D)[d_1\kappa_n + \tfrac{(\mu(D)+\eta)r-\eta g(D)}{\mu(D)+\eta+g(D)} - \tfrac{\eta g(D)}{\mu(D)+\eta}].
\end{aligned}$$

Lemma 3.9. *If $g(D) < (1 + \frac{\mu(D)}{\eta})r$, then E^* is locally asymptotically stable when $\tau = 0$.*

Proof. When $\tau = 0$, (3.7) becomes

$$\lambda^2 + (\tilde{a}_{1,n} + \tilde{b}_{1,n})\lambda + \tilde{a}_{0,n} + \tilde{b}_{0,n} = 0, \text{ for } n \in \mathbb{N}_0.$$

Because

$$\tilde{a}_{1,n} + \tilde{b}_{1,n} = (d_1 + d_2)\kappa_n + \frac{\mu(D)g(D)}{\mu(D) + \eta} + \frac{(\mu(D) + \eta)r - \eta g(D)}{\mu(D) + \eta + g(D)} + \eta + \mu(D) > 0$$

and

$$\tilde{a}_{0,n}+\tilde{b}_{0,n} = d_1 d_2 \kappa_n^2 + \{(\mu(D)+\eta)d_1 + [\frac{\mu(D)g(D)}{\mu(D) + \eta} + \frac{(\mu(D) + \eta)r - \eta g(D)}{\mu(D) + \eta + g(D)}]d_2\} + (\mu(D)+\eta)r - \eta g(D) > 0,$$

so all the roots of (3.7) have negative real parts when $\tau = 0$. This implies that E^* is asymptotically stable when $\tau = 0$. □

Suppose (3.7) has a pair roots $\pm \mathrm{i}\tilde{\omega}(\tilde{\omega} > 0)$ for some $\tau > 0$ and $n \in \mathbb{N}_0$, we get

$$-\tilde{\omega}^2 + \tilde{a}_{1,n}\mathrm{i}\tilde{\omega} + \tilde{a}_{0,n} + (\tilde{b}_{1,n}\mathrm{i}\tilde{\omega} + \tilde{b}_{0,n})(\cos\tilde{\omega}\tau - \mathrm{i}\sin\tilde{\omega}\tau) = 0.$$

Separating the real and imaginary parts,it gives

$$\begin{cases} \tilde{\omega}^2 - \tilde{a}_{0,n} = \tilde{b}_{1,n}\tilde{\omega}\sin\tilde{\omega}\tau + \tilde{b}_{0,n}\cos\tilde{\omega}\tau, \\ \tilde{a}_{1,n}\tilde{\omega} = \tilde{b}_{0,n}\sin\tilde{\omega}\tau - \tilde{b}_{1,n}\tilde{\omega}\cos\tilde{\omega}\tau. \end{cases} \tag{3.8}$$

Squaring each sides of the first equation above and plus them, we have

$$\tilde{\omega}^4 + (\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)\tilde{\omega}^2 + \tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 = 0. \tag{3.9}$$

Denote $\tilde{z} = \tilde{\omega}^2$, (3.9) can be rewritten as

$$\tilde{z}^2 + (\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)\tilde{z} + \tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 = 0. \tag{3.10}$$

(3.10) has two roots

$$\tilde{z}_n^{\pm} = \frac{1}{2}\left[2\tilde{a}_{0,n} + \tilde{b}_{1,n}^2 - \tilde{a}_{1,n}^2 \pm \sqrt{(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2)}\right].$$

If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 < 0$, (3.10) has a positive root $\tilde{z}_n^+$. If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 \geq 0$, $\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 < 0$ and $(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) \geq 0$, (3.10) has two positive roots $\tilde{z}_n^{\pm}$.

Denote $\tilde{\omega}_n^{\pm} = \sqrt{\tilde{z}_n^{\pm}}$,

$$\mathcal{D}_4 = \{n \in \mathbb{N}_0 | \tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 < 0\},$$

$$\mathcal{D}_5 = \{n \in \mathbb{N}_0 | \tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 > 0,\ \tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 < 0 \text{ and } (\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) > 0\},$$

$$\mathcal{D}_6 = \{n \in \mathbb{N}_0 | \tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 > 0,\ \tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 < 0 \text{ and } (\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) = 0\},$$

$$\tilde{\tau}_{j,n}^{\pm} = \begin{cases} \frac{1}{\tilde{\omega}_n^{\pm}} \left[\arccos \frac{(\tilde{\omega}_n^{\pm 2} - \tilde{a}_{0,n})\tilde{b}_{0,n} - \tilde{a}_{1,n}\tilde{b}_{1,n}\omega_n^{\pm 2}}{\tilde{b}_{0,n}^2 + \tilde{b}_{1,n}^2 \tilde{\omega}_n^{\pm 2}} + 2j\pi \right], & \sin \tilde{\omega}_n^{\pm} \tilde{\tau}_{j,n}^{\pm} \geq 0, \\ \frac{1}{\tilde{\omega}_n^{\pm}} \left[-\arccos \frac{(\tilde{\omega}_n^{\pm 2} - \tilde{a}_{0,n})\tilde{b}_{0,n} - \tilde{a}_{1,n}\tilde{b}_{1,n}\tilde{\omega}_n^{\pm 2}}{\tilde{b}_{0,n}^2 + \tilde{b}_{1,n}^2 \tilde{\omega}_n^{\pm 2}} + 2(j+1)\pi \right], & \sin \tilde{\omega}_n^{\pm} \tilde{\tau}_{j,n}^{\pm} < 0, \end{cases}$$

where $\sin \tilde{\omega}_n^{\pm} \tilde{\tau}_{j,n}^{\pm} = \frac{(\tilde{\omega}_n^{\pm 2} - \tilde{a}_{0,n})\tilde{b}_{1,n}\tilde{\omega}_n^{\pm} - \tilde{a}_{1,n}\tilde{b}_{0,n}\tilde{\omega}_n^{\pm}}{\tilde{b}_{0,n}^2 + \tilde{b}_{1,n}^2 \tilde{\omega}_n^{\pm 2}}$, $j \in \mathbb{N}_0$, $n \in \mathcal{D}_4$ or $n \in \mathcal{D}_5 \cup \mathcal{D}_6$.

Let $\lambda_n = \tilde{\alpha}_n(\tau) \pm \mathrm{i}\tilde{\omega}_n(\tau)$ be a pairs root of (3.3) for some $n \in \mathbb{N}_0$, then we have following conclusion.

Lemma 3.10. *For characteristic equations* (3.3)*, we have*

(i) $\tilde{\alpha}_n'(\tilde{\tau}_{n,j}^{+}) > 0$ *for* $n \in \mathcal{D}_4$.

(ii) $\tilde{\alpha}_n'(\tilde{\tau}_{n,j}^{+}) > 0$ *and* $\alpha_n'(\tilde{\tau}_{n,j}^{-}) < 0$ *for* $n \in \mathcal{D}_5$.

(iii) $\tilde{\alpha}_n'(\tilde{\tau}_{n,j}^{\pm}) = 0$ *for* $n \in \mathcal{D}_6$.

Proof. Similar to the proof of lemma 3.2, we have

$$\mathrm{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right)^{-1}|_{\tau=\tilde{\tau}_{j,n}^{\pm}} = \frac{\pm\sqrt{(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2)}}{\tilde{b}_{0,n}^2 + \tilde{b}_{1,n}^2 \tilde{\omega}_n^{\pm 2}}.$$

Since $\mathrm{sign}\left\{\tilde{\alpha}_n'(\tilde{\tau}_{j,n}^{\pm})\right\} = \mathrm{sign}\left\{\mathrm{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right)^{-1}|_{\tau=\tilde{\tau}_{j,n}^{\pm}}\right\}$, we can verify the conclusion. □

Denote

$$\tilde{\tau}_1^* = \min_{n \in \mathcal{D}_4} \{\tilde{\tau}_{0,n}^{+}\},\ \tilde{\tau}_2^* = \min_{n \in \mathcal{D}_5 \cup \mathcal{D}_6} \{\tilde{\tau}_{0,n}^{\pm}\},\ \tilde{\tau}^* = \min\{\tilde{\tau}_1^*, \tilde{\tau}_2^*\}.$$

From Lemma 3.9, 3.10 and the obvious argument, we have the following lemma.

Lemma 3.11. *If* $g(D) < (1 + \frac{\mu(D)}{\eta})r$*, we have*

(i) If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 \geq 0$ *and* $\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 \geq 0$ *or* $(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) < 0$*, then all root of* (3.7) *have negative real part for* $\tau \geq 0$.

(ii) If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 < 0$ *or* $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 \geq 0$, $\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 < 0$ *and* $(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) \geq 0$ *for some* $n \in \mathbb{N}_0$*, then then all root of* (3.7) *have negative real part for* $\tau \in [0, \tilde{\tau}^*)$.

(iii) If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 < 0$ *for some* $n \in \mathbb{N}_0$*, then* (3.7) *has a pair purely imaginary roots when* $\tau = \tilde{\tau}_{j,n}^+$.

(iv) If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 \geq 0$, $\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 < 0$ *and* $(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) \geq 0$ *for some* $n \in \mathbb{N}_0$*, then* (3.7) *has a pair purely imaginary roots when* $\tau = \tilde{\tau}_{j,n}^{\pm}$.

From Lemma 3.10 and 3.11, we have the theorem.

Theorem 3.12. *Suppose* $g(D) < (1 + \frac{\mu(D)}{\eta})r$*, then*

(i) If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 \geq 0$ *and* $\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 \geq 0$ *or* $(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) < 0$*, then* E^* *is locally asymptotically stable for* $\tau \geq 0$.

(ii) If $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 < 0$ *or* $\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2 \geq 0$, $\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2 < 0$ *and* $(\tilde{a}_{1,n}^2 - 2\tilde{a}_{0,n} - \tilde{b}_{1,n}^2)^2 - 4(\tilde{a}_{0,n}^2 - \tilde{b}_{0,n}^2) \geq 0$ *for some* $n \in \mathbb{N}_0$*, then* E^* *is locally asymptotically stable for* $\tau \in [0, \tilde{\tau}^*)$.

(iii) System (3.1) *undergoes Hopf bifurcation at* E^**, when* $\tau = \tilde{\tau}_{j,n}^+ (\tau = \tilde{\tau}_{i,n}^{\pm})$*, for* $n \in \mathcal{D}_4 (n \in \mathcal{D}_5)$ *and* $j \in \mathbb{N}_0$.

3.2 Simulation with glioma data

In this subsection, we perform numerical simulations to demonstrate our analytical results. We first provide a brief parameter study related to brain tumor gliomas, and then give two examples with medical implications.

We consider the space as one-dimensional space $(0, \pi)$, the radiation dose range from 1 to 60 Gy. The other parameters are obtained from the literature and our estimations. The parameters are summarized in Table 1.

Harpold et al pointed out that the diffusion coefficient of glioma cells and that of resistant glioma cells are different by about 10 times [29]. Rockne et al provided some estimations for the range of the diffusion coefficient which is 6 - 326 mm^2 per year, and the range of the glioma growth rate with spatial consideration which is 1 - 32 per year [17]. There are other studies in the literature which provided different

Table 1: Parameter setting in simulation

Parameters	Value	Units	Reference
α	0.02-0.2	1/Gy	[33]
α/β	4-10	Gy	[33]
$g(D)$	0.01-1.8	1/day	[34]
$\mu(D)$	0.1-2	1/day	[23], [34]
d_1	0.03-0.53	mm/day	[17], [29]
d_2	0.03-0.53	mm/day	[17], [29]
η	0.02-0.2	1/day	[33]
$1/r$	15-21	day	[34]
K	$50-100$	1/mm	estimated
τ	1-20	day	estimated

values for these parameters. If we use days or hours as the time unit, it is easy to get a rough range of glioma cell diffusion coefficient and the glioma spatial density growth rate under units of days or hours.

Leeuwen et al provided some detailed estimations for radiation parameters α and β. The α has a range from 0.02 to 0.2 Gy^{-1} and the ratio $\frac{\alpha}{\beta}$ has a range from 4 to 10 [33]. Yamashita et al estimated the glioma cell doubling time which is 15 - 21 days [34]. The radiation dose range from 1 to 60 Gy. Using these data, it is easy to obtain a rough range for $g(D)$ which is from 0.01 to 1.8.

The value $\frac{1}{\alpha}$ is an average life time of damaged tumor cells. The death rate of damaged tumor cells η is α. The damaged tumor cell repairing rate $\mu(D)$ is estimated by the repair time which is several hours to 2 days [23].

In the 3 dimensional space, it is known that the cell density of animal tissue is about 10^6 cells per mm^3. If we consider 1 dimension space, this constant is 10^2 cells per mm. All parameter values are taken articles mentioned above.

Example 3.13 illustrates the situation where the tumor can be destroyed by radiotherapy, and Turing instability may occur under certain conditions. Example 3.14 illustrates the situation where radiotherapy may not completely destroy the tumor, however, there may occur periodic oscillations between tumor cells and damaged tumor cells with certain period of repair time.

Example 3.13. Let $d_1 = 0.5,\ d_2 = 0.05,\ K = 100,\ r = 0.05,\ \mu(D) = 0.5,\ \eta =$

0.1, $g(D) = 0.7$. From calculation, we find for (3.5) has positive roots

$$\omega_1^+ = 0.1369,\ \omega_2^+ = 0.2147.$$

So we get

$$\tau_{1,j}^+ = 27.0627 + 45.9011j,\ \tau_{2,j}^+ = 17.3881 + 29.2585j,$$

for $j \in \mathbb{N}_0$. $\tau^* = \tau_{2,0}^+ = 17.3881$ days.

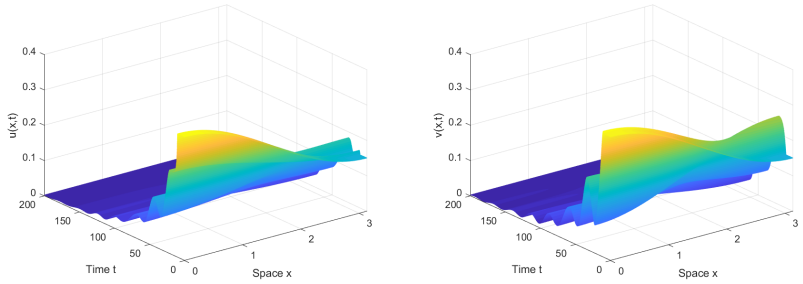

Figure 2: There exists an asymptotically stable solution, where $\tau = 10 < \tau^*$.

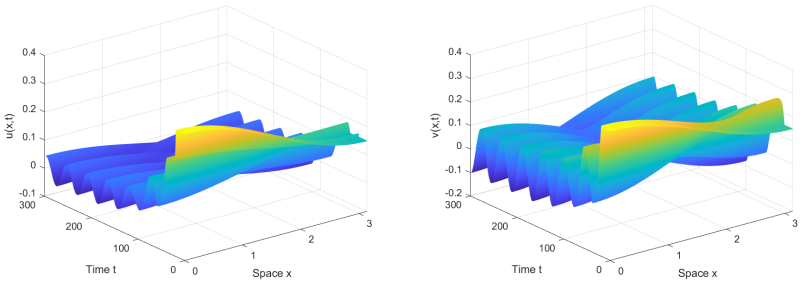

Figure 3: E_0 is Turing unstable, where $\tau = 18 > \tau^*$.

We compute the radiation threshold value $R = (1+\frac{\mu(D)}{\eta})r = 0.3$, and the radiation rate $g(D) = 0.7$ which is greater than the radiation threshold. From Theorem 3.5 and 3.6, the steady state $E_0 = (0, 0)$ is locally asymptotically stable when $\tau < \tau^*$ (see Fig.2). In this case, we may interpret that the radiation therapy destroys the tumor if the damaged tumor cell repair time is smaller than the critical time $\tau^* = 17.3881$ days. When the damaged tumor cell repair time is longer than $\tau^* = 17.3881$ days, we observe oscillations of tumor cell population and damaged tumor cell population. We do not show the oscillation case. From Theorem 3.8, we know that when $\tau > \tau^*$,

E_0 is Turing unstable (see Fig.3). Although we conclude that radiotherapy destroys the tumor when $g(D) > R$, the damaged tumor cell repair time τ can complicate outcomes of radiotherapy.

Example 3.14. Let $d_1 = 0.5,\ d_2 = 0.05,\ K = 100,\ r = 0.05,\ \mu(D) = 0.5,\ \eta = 0.1,\ g(D) = 0.2$. For this set of parameter values we observe that the assumption of Theorem 3.12 holds. From calculation, we find for (3.9) has positive roots

$$\tilde{\omega}_0^+ = 0.4598,\ \tilde{\omega}_0^- = 0.0382,\ \tilde{\omega}_1^+ = 0.3286.$$

So we get

$$\tilde{\tau}_{0,j}^+ = 4.8013 + 13.6642,\ \tilde{\tau}_{0,j}^- = 123.06735 + 164.5373j,\ \tilde{\tau}_{1,j}^+ = 12.1914 + 19.1185j,$$

for $j \in \mathbb{N}_0$. $\tilde{\tau}^* = \tilde{\tau}_{0,0}^+ = 4.8013$ days.

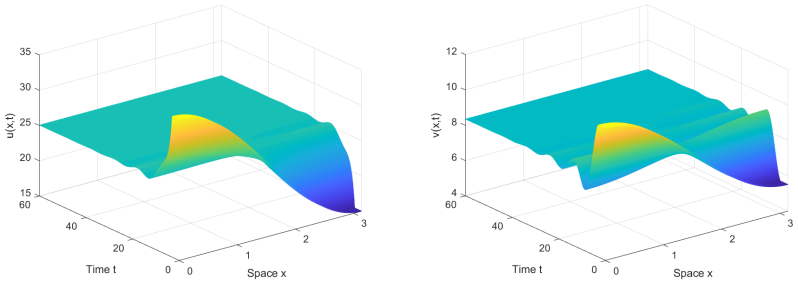

Figure 4: There steady state $E^* = (25, 8.3333)$ when $\tau = 3 < \tilde{\tau}^*$.

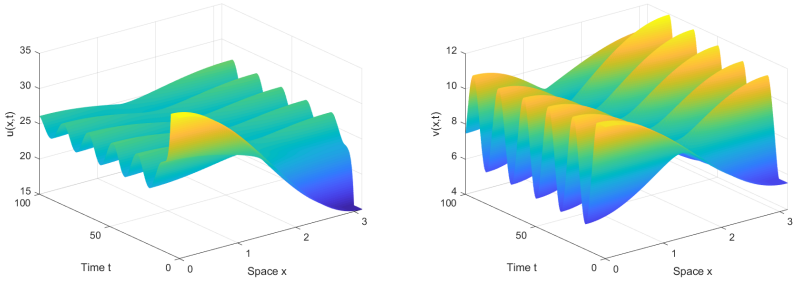

Figure 5: There exists an orbitally stable periodic solution when $\tau = 6 > \tilde{\tau}^*$.

We compute the radiation threshold $R = 0.3$, and $g(D) = 0.2$ which is below the threshold. So from Theorem 3.12, the positive spatially uniform steady state

$E^* = (25, 8.3333)$ is locally asymptotically stable when $\tau < \tilde{\tau}^*$ and $\tilde{\tau}^* = 4.8013$ days, and we show this case in Fig.4. The system (3.1) undergoes a Hopf bifurcation at E^*, when $\tau = \tilde{\tau}^{\pm}_{0,j}$ or $\tilde{\tau}^{+}_{1,j}$, for $j \in \mathbb{N}_0$. We show this case in Fig.5. For the set of the parameter values, we see $u^* + v^* = 25 + 8.3333 = 33.3333 = (1 - \frac{g(D)}{R})K$. If we increase the radiation dose D, then the tumor load of steady state u^*+v^* will decrease because $g(D)$ is an increasing function of the radiation dose D. We do not present these figures for different radiation dosage here. We also notice that, the critical time $\tilde{\tau}^*$ for oscillation occurrences in this case is shorter than that τ^* in Example 3.13. A possible biological explanation is that, when the radiation rate $g(D)$ is greater than its threshold R which is strong, the strong radiation may suppress damaged tumor cell recovering and take more time for damaged tumor cells repairing.

4 Discussion and implications

In this work, we proposed and studied a functional reaction diffusion model for radiotherapy. The purpose of our study was to understand how damage process and repair process affect the outcomes of radiotherapy. In particular, we would like to know how damage process and repair process change conventional radiation dosage because previous mathematical models have not incorporated those two processes together. Our model is based on established tumor growth models and radiotherapy models. The distinguished character of our model is that we incorporate the repair process of damaged cells into the model and the repair time of damaged tumor cells as a delay parameter.

The radiation rate $g(D)$ was easily derived from Lea's target theory [28]. It is an increasing function of radiation dose D. We derived a combined parameter $R(D) = (1 + \frac{\mu(D)}{\eta})r$, where η is the damaged cell death rate and $\mu(D)$ is the rate of damaged cell becoming proliferating cells or damaged cell repair rate, which is essentially the survival probability. $\mu(D)$ was also easily derived from Lea's target theory, and we can also apply LQ model to obtain $\mu(D)$ [14]. The quantity $\frac{1}{\eta}$ may be considered as the average survival time of damaged tumor cells. This combined parameter $R(D)$ can describe a total growth rate of the tumor under irradiation, which is a decreasing function of radiation dose D. It serves as a threshold value of the radiation rate $g(D)$, and may also be called the functional radiation threshold. Lemma 3.1 says that, if we take the damaged tumor repair time τ to be zero, radiotherapy will

kill the tumor when the radiation rate $g(D)$ is greater than the radiation threshold $R(D)$. However, the repair time is not zero in reality. We then found a critical time τ^* stated in Theorem 3.5, and radiation still can kill the tumor if the repair time is less than τ^*. If the repair time is greater than τ^*, the proliferating cell population and damaged cell population will oscillate periodically. We also observe Turing instability. That is, we observe some areas of the tumor site have no tumor cells but damaged cells and some other areas of the tumor site have no damaged cells but tumor cells. The similar phenomena in tumor radiation therapy was also observed in [1]. The conditions to have such Turing instability are stated in Theorem 3.8, which is that the radiation rate is greater than the functional radiation threshold, the proportion rate of damaged cells recovering is greater than the damaged cell death rate, and the ratio of the diffusion coefficient of proliferating cells to that of damaged cells is within some range of values. Overall, if the radiation damage rate is greater than the functional radiation threshold, radiotherapy may destroy the tumor.

When the radiation damage rate $g(D)$ is smaller than the functional radiation threshold $R(D)$, the model has another spatially uniform steady state $E^* = (u^*, v^*)$ where the tumor cells and damaged cells both exist, and the total tumor load is $u^* + v^* = (1 - \frac{g(D)}{R})K$ which is smaller than the tumor capacity K. Lemma 3.9 says that, if we take the repair time to be zero, then this steady state is asymptotically stable. Biologically, this means that the radiotherapy may control the tumor growth. However, repairing damaged cells takes some time. When the repair time is less than another critical value $\tilde{\tau}^*$, we can still control the tumor growth. If the repair time is longer than this critical value, we may observe periodical oscillations of two populations as stated in Theorem 3.12. An overall medical implication is that, if the radiation damaged rate is smaller that the radiation threshold, radiotherapy may control the tumor growth; as the radiation dose increases, the tumor load will decrease.

As the model predictions, the repair time plays an important role in radiotherapy. In two case, the radiation damaged rate $g(D)$ is greater or smaller than the functional radiation threshold $R(D)$, there exist two critical repair times beyond which the radiation therapy show two cell populations oscillation behaviors and Turing patterns. This complicates the radiation therapy. A medical implication could be that shortening damaged cell repair time may improve efficacy of irradiation.

We also notice that the functional radiation threshold $R(D) = (1 + \frac{\mu(D)}{\eta})r$ is

greater that the tumor growth rate r, in general, because of the ratio $\frac{\mu(D)}{\eta}$ of the damaged tumor cell repair rate to the damaged tumor cell death rate. If we want radiotherapy to destroy the tumor, the radiation rate $g(D)$ should be higher than that without repair process of damaged tumor cells. For some tumor cells, they may have a sophisticated repair process of damaged tumor cells; for other tumor cells, their damaged cell repair process may be simple. This may explain different tumors need different radiation dosages. In other words, the damaged tumor cell repair process increases the radiation threshold. If this process was neglected, the radiation threshold would be $R = r$. This reveals that the radiation dose may be underestimated when the damaged cell repair does not counted for radiotherapy.

Damaged cell repair as well as the radiation damaging events is stochastic in nature. The repair time varies for different cells. The damaged cell repair time may be approximated by a random variable. However, as an approximation, we consider the repair time to be a parameter. Our analysis shows radiotherapy may destroy or control the tumor if the repair time is less than critical values, and it may induce oscillations when the repair time is longer.

As we discuss above, our results may have following two potential applications. In tumor precise radiotherapy, we may set up a functional radiation threshold according to different types of tumors and different patients because this function has the tumor growth rate and damaged tumor cell death rate as its arguments, and then using the radiation damage rate (which is a function of radiation dose) and the functional radiation threshold to make a precise radiation dosage schedule for a particular patient. In general radiobiology, according to different types of cells, for example, different types of human cells, different types of animal cells, and different types of plant cells, functional radiation thresholds can be established, and then based on our study, a radiation dosage schedule can be set up to obtain expected radiation results.

Instead of finite-time simulations of mathematical models for radiotherapy, we conduct asymptotical analysis of our model. This analysis provides certain insights about radiotherapy. To further our study, we will follow two directions: consider the delay parameter of the repair time is a random variable with certain density distribution, and consider radiotherapy in our model as a finite-time perturbation to conduct analysis with experimental comparisons.

5 Conclusions

The damaged tumor cell repair process increases the functional radiation threshold and complicates outcomes of radiotherapy. The medical implication of our results is in precise radiotherapy where a radiation dosage schedule could be made according to particular type of tumors to gain a maximum efficacy. Our results may also be applied in radiobiology in a similar manner.

List of abbreviations

- DNA: deoxyribonucleic acid
- LQ: linear quadratic
- ODE: ordinary differential equation
- PDE: partial differential equation

Declarations

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