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Stability of a mathematical model of tumor-induced angiogenesis*

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Abstract. A model consisting of three differential equations to simulate the interactions between cancer cells, the angiogenic factors and endothelial progenitor cells in tumor growth is developed. Firstly, the global existence, nonnegativity and boundedness of the solutions are discussed. Secondly, by analyzing the corresponding characteristic equations, the local stability of three boundary equilibria and the angiogenesis equilibrium of the model is discussed, respectively. We further consider global asymptotic stability of the boundary equilibria and the angiogenesis equilibrium by using the well-known Liapunov–LaSalle invariance principal. Finally, some numerical simulations are given to support the theoretical results.

Keywords: cancer, angiogenic factors, time delay, stability.

1 Introduction

Cancer progression occurs first through the generation and growth of a single tumor in a specific site. Over time, the tumor progresses to higher degrees of malignancy and spreads to other organs by a process known as metastasis [2, 7]. Metastasis spread is the predominant cause of cancer-induced death.

Once tumor cells have settled at a site, they often remain dormancy and grow up to about 2 mm in a diameter and then remaining at that size. Within the mass of the tumor, cell replication is balanced by programmed cell death. Unfortunately, tumors do not tend to stay in this state but progress to a mode of accelerated growth, to the detriment of the surrounding tissue. This abnormally high growth rate soon outpaces the

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supply of oxygen and nutrients from the host's vasculature [8]. Consequent changes in the cells of the tumor lead to the release of diffusible proteins (angiogenic factors) from the tumor or its immediate vicinity. These proteins spread through the surrounding tissue, forming attachments with structures (receptors) that protrude from the cells of nearby blood vessels. The attachment initiates a cascade of processes leading to the formation of blood vessel sprouts. This is tumor-induced angiogenesis [20, 24]. The new blood vessels supply nutrients, oxygen and access to routes by which tumor cells may travel to other sites within the host (metastasize). As the tumor vasculature is a key element of the tumor stroma, angiogenesis is the target of many cancer therapies.

Consequently, new blood supply is formed and the tumor can progress. There are two basic ways in which angiogenesis can occur. (i) First, it is believed that the angiogenic promoters induce existing and differentiated endothelial cells [3, 19], which make up the current blood supply, to divide and form new blood vessels [11, 13]. (ii) The second mechanism is that the recruitment of endothelial cells by promoters. The most critical growth factor associated with angiogenesis, in particular tumor angiogenesis, is arguably vascular endothelial growth factors (VEGF). Recently, many studies have found evidence that this might be a prominent mechanism by which new blood supply is formed for tumors [31].

The determination that tumor growth was dependent on angiogenesis, made in 1971 by Folkman [9], led to the hope that disruption of angiogenesis could form the basis for effective cancer treatments. Since then the study of tumor-induced angiogenesis and anti-angiogenesis has grown into a huge area of biological and medical research.

A schematic diagram describing the process of tumor angiogenesis is shown in Fig. 1 [16], which can be divided into four different stages. A small, dormant tumor (stage 1) can depend on the nature of the tumor and its microenvironment, make the angiogenic switch to ensure exponential growth. The tumor secretes angiogenic growth factors to activate endothelial cells of surrounding vessels (stage 2). Upon activation, these endothelial cells start to migrate and proliferate toward the tumor. Only one endothelial cell starts an angiogenic sprout and develops into an endothelial tip cell migrating along the extracellular matrix (ECM) and guiding the following so-called stalk endothelial cells (stage 3) [1, 12]. Finally, the growing tumor is connected to the vasculature (stage 4). In addition to growth and proliferation, the tumor can metastasize. Malignant tumor cells, by invading the vessels, ECM degradation, attachment, and homing to target sites can form distal metastases [4].

In recent decades, an abundance of biological research has focused on tumor-induced angiogenesis in the hope that treatments targeted at the vasculature may result in a stabilisation or regression of the disease: a tantalizing prospect. The complex and fascinating process of angiogenesis has also attracted the interest of researchers in the field of mathematical biology, a discipline that is, for mathematics, relatively new. The challenge in mathematical biology is to produce a model that captures the essential elements and critical dependencies of a biological system. Such a model may ultimately be used as a predictive tool. In order to affect the angiogenic process, an anti-angiogenic agent is introduced in many treatments [9, 10, 15, 21, 22]. It happens that anti-angiogenic is particularly efficient for slow growing solid tumors [1]. In [23], an ODE model that does not consider an angiogenesis promoter factors compartment is investigated, in [31],

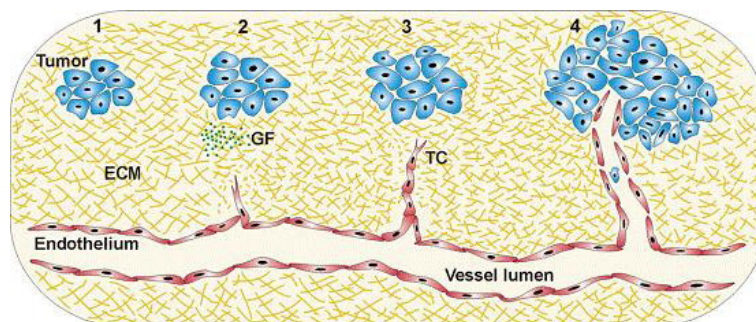


Figure 1. The sequential steps during tumor angiogenesis.

a model, which describes the growth of a single angiogenic tumor is investigated, and then generalize this model to include multiple tumors, which compete for circulating endothelial cells in order to build new blood vessels. In [5], they give a special issue on cancer modelling, analysis and control. In [34], they present a continuous model for three early stage events in angiogenesis: initiation, sprout extension and vessel maturation. More works on tumor angiogenesis can be found in [25, 26, 27].

Generally, the dynamic behaviors of various mathematical models are usually handled by the classical theories and methods on delay differential equations, like constructing Lyapunov functionals [6, 17, 28, 29, 33], Lyapunov–LaSalle invariance principle [30, 32] and so on. By using these techniques, we give a complete global stability analysis for delay differential equation model (1).

The paper is structured as follows. In the next section, we develop our model. In Section 3, we discuss the global existence, nonnegativity, boundedness of solutions, nature of equilibria. By analyzing the corresponding characteristic equations, the local stability of three boundary equilibria and the positive equilibrium of the system is discussed, respectively. In Section 4, we further consider global asymptotic stability of the boundary equilibria and the positive equilibrium by using the well-known Liapunov–LaSalle invariance principle. In Section 5, some numerical simulations are given to illustrate the results found.

2 The model

We now present our model of interactions between cancer cells, angiogenic growth factors and endothelial cells. Let $T(t)$ and $E(t)$ be the mass of cancer cells and endothelial cells, respectively. The angiogenic growth factor concentration is denoted by $P(t)$. The model is based on the considerations discussed in the introduction, which we summarize below:

1. The tumor growth rate is density-dependent and the cancer cells cannot exceed an upper limit, denoted by k . In addition, the growth of cancer cells is dependent on the presence of the endothelial cells [23] (the term $rT(t)(1 - T(t)/(k + \Gamma E(t)))$).
2. Angiogenesis is induced by the release of various pro-angiogenic cytokines by the tumor cells.

3. The endothelial cells $E(t)$ exhibit logistic proliferation rates, the other growth is a proliferation term whereby endothelial cells are stimulated by angiogenic growth factors, that is, produced by cancer cells, according to Holling type 2 function [18] (the term $\beta E(t)P(t)/(g + P(t))$).
4. There is a time delay necessary for the production of the angiogenic growth factors stimulated by cancer cells to form.

Hence, we obtain the following model:

$$\begin{aligned}\dot{T}(t) &= rT(t)\left(1 - \frac{T(t)}{k + \Gamma E(t)}\right) - dT(t), \\ \dot{P}(t) &= \alpha T(t - \tau) - hP(t), \\ \dot{E}(t) &= cE(t)(1 - bE(t)) + \frac{\beta E(t)P(t)}{g + P(t)} - \mu E(t).\end{aligned}\tag{1}$$

In accordance with the biological meaning, the initial functions of model (1) is taken as follows:

$$T(\theta) = \phi_1(\theta), \quad P(\theta) = \phi_2(\theta), \quad E(\theta) = \phi_3(\theta), \quad \theta \in [-\tau, 0],\tag{2}$$

where $\phi_i(\theta)$ are continuous and nonnegative on $[-\tau, 0]$ ($i = 1, 2, 3$), that is, $\phi = (\phi_1, \phi_2, \phi_3)^T \in C = C([- \tau, 0], \mathbb{R}_+^3)$, where C is a Banach space with norm $\|\phi\| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|$.

The parameters in model (1) may be interpreted as follows. r and k are the proliferation rates and carrying capacities of $T(t)$. Γ is the proportion of endothelial cells responsible for the tumor angiogenesis. Cancer cells die with a rate d . Angiogenic factors are produced by cancer cells with a rate α and decay with a rate h . c and $1/b$ are the proliferation rates and carrying capacities of $E(t)$. The population of the endothelial cells die with a rate μ . β is the rate at which the endothelial cells grows and g is the half saturation constant. τ represents the time taken for the cancer cells to stimulate the angiogenic growth factors to form.

By using the basic theory of delay differential equations (see [14]) and some simple calculation, it is not difficult to show the following theorem.

Theorem 1. *The solution $(T(t), P(t), E(t))$ of model (1) with the initial condition (2) exists, is unique and nonnegative on $[0, +\infty)$, and satisfies*

$$\begin{aligned}\limsup_{t \rightarrow \infty} T(t) &\leq \frac{kbc + \Gamma(c + \beta)}{bc} \equiv T_M, \\ \limsup_{t \rightarrow \infty} P(t) &\leq \frac{\alpha(kbc + \Gamma(c + \beta))}{hbc} \equiv P_M, \\ \limsup_{t \rightarrow \infty} E(t) &\leq \frac{c + \beta}{bc} \equiv E_M.\end{aligned}$$

In addition, $G = \{\phi = (\phi_1, \phi_2, \phi_3) \in C \mid 0 \leq \phi_1 \leq T_M, 0 \leq \phi_2 \leq P_M, 0 \leq \phi_3 \leq E_M\}$ attracts all solutions of model (1) and is positively invariant.

3 Local stability analysis

3.1 Existence of equilibria

Next, we examine the conditions under which a tumor can grow and expand. As model (1) is formulated, it assumes that the tumor can grow only if sufficient blood supply is generated. Therefore, model (1) describes the growth of angiogenic cells. Nonangiogenic cells cannot grow beyond a very small size. Such nonangiogenic cells are not explicitly included in the model. Thus, if the angiogenic tumor cells go extinct in the model, this does not mean that the entire population of tumor cells goes extinct, but that only a small number of cells remain.

We now find all biologically feasible equilibria admitted by model (1) and study the dynamic properties of the model around each equilibrium. The equilibria for model (1) are as follows:

- (i) There always exists the trivial equilibrium $F_0 = (0, 0, 0)$. In this case, the angiogenic cells cannot grow and go extinct, all populations are extinct.
- (ii) If $c > \mu$, there exists a tumor-free equilibrium $F_1 = (0, 0, \bar{E})$, where $\bar{E} = (c - \mu)/(bc)$. In this case, the tumor cell population is zero but the endothelial cells survive.
- (iii) If $r > d$, there exists an endothelium-free equilibrium $F_2 = (\hat{T}, \hat{P}, 0)$, where $\hat{T} = k(r - d)/r$, $\hat{P} = \alpha k(r - d)/(rh)$. In this case, the angiogenic factors, which are produced by cancer cells, cannot promote the additional endothelial cells.

In mathematics, the equilibria F_0, F_1, F_2 are also called the boundary equilibria.

- (iv) Model (1) has an angiogenesis equilibrium provided that $r > d$ and the quadratic equation

$$\alpha\Gamma bc(r - d)E^2 - (\alpha\Gamma(r - d)(c - \mu + \beta) - bc(grh + \alpha k(r - d)))E - (grh(c - \mu) + \alpha k(r - d)(c - \mu + \beta)) = 0 \tag{3}$$

has a positive root.

Next, we give the conditions to ensure that (3) has the positive root under $r > d$. If

$$r > d \quad \text{and} \quad grh(c - \mu) + \alpha k(r - d)(c - \mu + \beta) > 0, \tag{4}$$

then equation (3) has a unique positive root. If

$$\begin{aligned} r > d, \quad & grh(c - \mu) + \alpha k(r - d)(c - \mu + \beta) < 0, \\ & \alpha\Gamma(r - d)(c - \mu + \beta) - bc(grh + \alpha k(r - d)) > 0, \\ & (\alpha\Gamma(r - d)(c - \mu + \beta) + bc(grh + \alpha k(r - d)))^2 \\ & - 4\alpha\Gamma bcgrh\beta(r - d) > 0, \end{aligned} \tag{5}$$

then (3) has two different positive roots.

From the above, we have the following.

Lemma 1. *If (4) holds, there exists a unique angiogenesis equilibrium $F^* = (T^*, P^*, E^*)$, where E^* is the root of equation (3) and*

$$T^* = \frac{(r-d)(k + \Gamma E^*)}{r}, \quad P^* = \frac{\alpha(r-d)(k + \Gamma E^*)}{rh}.$$

If (5) holds, there exist two angiogenesis equilibria $F^ = (T^*, P^*, E^*)$ and $F^{**} = (T^{**}, P^{**}, E^{**})$, where E^* and E^{**} are the solutions of equation (3).*

3.2 Characteristic equation

In order to determine the stability of any equilibrium $F(T, P, E)$, we linearize model (1) about F and obtain

$$w'(t) = Aw(t) + Bw(t - \tau),$$

where $w(t) = (T(t), P(t), E(t))^T$ and

$$A = \begin{bmatrix} r(1 - \frac{2T}{k + \Gamma E}) - d & 0 & \frac{\Gamma r T^2}{(k + \Gamma E)^2} \\ 0 & -h & 0 \\ 0 & \frac{g\beta E}{(g + P)^2} & c(1 - 2bE) + \frac{\beta P}{g + P} - \mu \end{bmatrix},$$

$$B = \begin{bmatrix} 0 & 0 & 0 \\ \alpha & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

where matrices A and B are computed at the equilibrium under consideration. The stability is determined by computing the roots of the characteristic equation

$$\det(\lambda I - A - Be^{-\lambda\tau}) = 0. \quad (6)$$

3.3 Local stability

From the point of view in disease management, it is important to identify the range of the parameters such that tumor cells can be eventually removed or exist forever. Hence, in mathematics, it is necessary to consider stability of the equilibria of model (1).

For local stability of the equilibria F_0 , F_1 and F_2 of model (1), we have the following results.

Theorem 2. *For model (1), we have:*

- (i) *If $r < d$ and $c < \mu$, then the trivial equilibrium F_0 is locally asymptotically stable for any time delay $\tau \geq 0$.*
- (ii) *If $r < d$ and $c > \mu$, then the tumor-free equilibrium F_1 is locally asymptotically stable for any time delay $\tau \geq 0$.*
- (iii) *If $r > d$ and $\alpha k(r-d)(c - \mu + \beta) + grh(c - \mu) < 0$, then the endothelium-free equilibrium F_2 is locally asymptotically stable for any time delay $\tau \geq 0$.*

Proof. The eigenvalues of model (1) at $F_0 = (0, 0, 0)$ are $\lambda_1 = r - d$, $\lambda_2 = -h < 0$, $\lambda_3 = c - \mu$. If $r < d$ and $c - \mu < 0$, all eigenvalues are negative and F_0 is locally asymptotically stable for any time delay $\tau \geq 0$.

The eigenvalues of model (1) at $F_1 = (0, 0, \bar{E})$ are $\lambda_1 = r - d$, $\lambda_2 = -h < 0$, $\lambda_3 = (c - \mu - 2bc\bar{E}) = \mu - c < 0$. If $r < d$ and $c > \mu$, all eigenvalues are negative and F_1 is locally asymptotically stable for any time delay $\tau \geq 0$.

The eigenvalues of model (1) at $F_2 = (\hat{T}, \hat{P}, 0)$ are

$$\lambda_1 = r - d - \frac{2r\hat{T}}{k} = -(r - d) < 0, \quad \lambda_2 = -h < 0,$$

$$\lambda_3 = c - \mu + \frac{\beta\hat{P}}{g + \hat{P}} = \frac{\alpha k(r - d)(c - \mu + \beta) + grh(c - \mu)}{grh + \alpha k(r - d)}.$$

If $\alpha k(r - d)(c - \mu + \beta) + grh(c - \mu) < 0$ and $r > d$, all eigenvalues are negative and F_2 is locally asymptotically stable for any time delay $\tau \geq 0$.

This completes the proof. □

From Lemma 1, we have that there exists a unique angiogenesis equilibrium $F^* = (T^*, P^*, E^*)$ if (4) holds and that there exist two angiogenesis equilibria $F^* = (T^*, P^*, E^*)$ and $F^{**} = (T^{**}, P^{**}, E^{**})$ if (5) holds. Without loss of generality, we assume that $F^* > F^{**}$. Next, we discuss local stability of the angiogenesis equilibria.

Theorem 3.

- (i) If $r > d$ and $c \geq \mu$ hold, the angiogenesis equilibrium F^* of model (1) is locally asymptotically stable for any time delay $\tau \geq 0$.
- (ii) If (5) holds, the angiogenesis equilibrium F^* of model (1) is locally asymptotically stable for any time delay $\tau \geq 0$.
- (iii) If (5) holds, the angiogenesis equilibrium F^{**} of model (1) is unstable for any time delay $\tau \geq 0$.

Proof. Computing the characteristic polynomial (6) at F^* , we obtain

$$H(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + b_0e^{-\lambda\tau} = 0, \tag{7}$$

where

$$a_2 = (r - d) + h + bcE^*,$$

$$a_1 = h(r - d) + hbcE^* + bc(r - d)E^*,$$

$$a_0 = hbc(r - d)E^*,$$

$$b_0 = - \frac{\Gamma r \alpha \beta g T^{*2} E^*}{(g + P^*)^2 (k + \Gamma E^*)^2}.$$

We first discuss the situation that the cancer cells stimulate the angiogenic growth factors to form is instantaneous (that is, $\tau = 0$), the characteristic equation (7) is reduced to

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + b_0 = 0. \tag{8}$$

Obviously, $a_2 > 0$.

If (4) holds, there exists a unique equilibrium F^* . Next, let us show that $a_0 + b_0 > 0$. From (3) and (4), it has

$$E^* \geq \frac{\Gamma\alpha\beta(r-d) - bc(ghr + \alpha k(r-d))}{2\alpha bc\Gamma(r-d)},$$

thus,

$$\begin{aligned} a_0 + b_0 &= \frac{T^*E^*}{(k + \Gamma E^*)(g + P^*)^2} (hrbcP^{*2} + 2hrbcgP^* + g(hrbcg - \Gamma\alpha\beta(r-d))) \\ &= \frac{T^*E^*}{(k + \Gamma E^*)(g + P^*)^2} (hrbcP^{*2} + 2bcg\alpha(r-d)(k + \Gamma E^*) \\ &\quad + ghrbcg - g\Gamma\alpha\beta(r-d)) \\ &> \frac{T^*E^*}{(k + \Gamma E^*)(g + P^*)^2} (hrbcP^{*2} + bcg(ghr + \alpha k(r-d)) \\ &\quad + 2bcg\alpha(r-d)\Gamma E^* - g\Gamma\alpha\beta(r-d)) > 0. \end{aligned}$$

If (5) holds, there exists two angiogenesis equilibria F^* and F^{**} ($F^{**} < F^*$). Next, we discuss the sign of $a_0 + b_0$ at F^* . Let

$$G(P) = hrbcP^2 + 2hrbcgP + g(hrbcg - \Gamma\alpha\beta(r-d)).$$

Then

$$a_0 + b_0 = \frac{T^*E^*}{(k + \Gamma E^*)(g + P^*)^2} G(P^*).$$

From equation (3) and Vieta's theorem, we have

$$\begin{aligned} E^* + E^{**} &= \frac{\alpha\Gamma(r-d)(c - \mu + \beta) - bc(ghr + \alpha k(r-d))}{\alpha\Gamma bc(r-d)}, \\ E^*E^{**} &= \frac{-(ghr(c - \mu) + \alpha k(r-d)(c - \mu + \beta))}{\alpha\Gamma bc(r-d)}. \end{aligned}$$

By the above expressions, Lemma 1 and $P^* > P^{**}$, we have

$$\begin{aligned} \frac{P^* + P^{**}}{2} &= \frac{\alpha\Gamma(r-d)(c - \mu + \beta) - bc(ghr - \alpha k(r-d))}{2hrbc} < P^*, \\ P^*P^{**} &= \frac{-g\alpha(r-d)(bck + \Gamma(c - \mu))}{hrbc} < P^{*2}. \end{aligned}$$

Since the function $G(P)$ is increasing for $P > 0$, we have

$$\begin{aligned} G(P^*) &> -g\alpha(r-d)(bck + \Gamma(c - \mu)) + \alpha g\Gamma(r-d)(c - \mu + \beta) \\ &\quad - bcg(ghr - \alpha k(r-d)) + ghrbcg - g\Gamma\alpha\beta(r-d) = 0. \end{aligned}$$

Hence, we have $a_0 + b_0 > 0$.

Now, let us further show that $a_2a_1 - (a_0 + b_0) > 0$. In fact, it has that

$$\begin{aligned} & a_2a_1 - (a_0 + b_0) \\ &= \frac{hrT^*}{k + \Gamma E^*} \left(h + \frac{rT^*}{k + \Gamma E^*} \right) + \left(h + \frac{rT^*}{k + \Gamma E^*} \right) \left(hbcE^* + \frac{rbcT^*E^*}{k + \Gamma E^*} \right) \\ & \quad + bcE^* \left(hbcE^* + \frac{rbcT^*E^*}{k + \Gamma E^*} \right) + \frac{\Gamma r\alpha\beta gT^{*2}E^*}{(g + P^*)^2(k + \Gamma E^*)^2} > 0. \end{aligned}$$

By Routh–Hurwitz criterion we know that all roots of (8) have negative real parts and $\lambda = 0$ is not the root of (8). If (7) has pure imaginary roots $\lambda = i\omega$ for some $\omega > 0$ and $\tau > 0$, we have from (7) that

$$-i\omega^3 - a_2\omega^2 + a_1i\omega + a_0 + b_0(\cos \omega\tau - i \sin \omega\tau) = 0.$$

Hence, we have

$$\begin{aligned} -\omega^3 + a_1\omega &= b_0 \sin \omega\tau, \\ a_2\omega^2 - a_0 &= b_0 \cos \omega\tau, \end{aligned} \tag{9}$$

which leads to

$$\omega^6 + p\omega^4 + q\omega^2 + r = 0, \tag{10}$$

where

$$p = a_2^2 - 2a_1, \quad q = a_1^2 - 2a_0a_2, \quad r = a_0^2 - b_0^2 > 0.$$

Let $v = \omega^2$, then (10) becomes

$$h(v) = v^3 + pv^2 + qv + r = 0. \tag{11}$$

Since

$$\begin{aligned} p &= (bcE^*)^2 + h^2 + \left(\frac{rT^*}{k + \Gamma E^*} \right)^2 > 0, \\ q &= \left(\frac{hrT^*}{k + \Gamma E^*} \right)^2 + (hbcE^*)^2 + \left(\frac{rbcT^*E^*}{k + \Gamma E^*} \right)^2 > 0, \end{aligned}$$

hence, we have that $h(v) > 0$, which contradicts $h(v) = 0$. This shows that all the roots of the characteristic equation (7) have negative real parts for any time delay $\tau \geq 0$. Therefore, the conclusions (i) and (ii) hold. By the similar argument as above, it has

$$\begin{aligned} P^{**} &< \frac{\alpha\Gamma(r - d)(c - \mu + \beta) - bc(gh - \alpha k(r - d))}{2hrbc}, \\ P^{**2} &< \frac{-g\alpha(r - d)(bck + \Gamma(c - \mu))}{hrbc}. \end{aligned}$$

Consequently, $G(P^{**}) < 0$. Hence, $a_0 + b_0 = T^{**}E^{**}G(P^{**}) / (k + \Gamma E^{**})(g + P^{**})^2 < 0$. For any time delay $\tau \geq 0$, $H(0) = a_0 + b_0 < 0$ and $\lim_{t \rightarrow +\infty} H(\lambda) = +\infty$. It has from

the continuity of the function $H(\lambda)$ on $[0, +\infty)$ that $H(\lambda) = 0$ has one positive root. Consequently, the characteristic equation (7) has one positive root. Thus, conclusion (iii) holds.

This completes the proof. \square

Remark 1. In Theorem 3(i), we give the conditions under which the tumor cells can grow and expand. As the model is formulated, it is assumed that the tumor cells can grow only if the blood supply is sufficient. Necessary conditions for the growth of tumor cells are $c \geq \mu$ and $r > d$. The growth of tumor cells is determined by the intrinsic rate of cell division r and the death rate of tumor cells d , and how many endothelial cells are available (expressed in the parameters c) and the death rate of endothelial cells μ . A high intrinsic rate of cell division, a low death rate of tumor cells, and a large available of endothelial cells promotes the growth of cancer cells.

4 Global stability

4.1 Global asymptotic stability of the boundary equilibria

In this section, we will consider the global asymptotic stability of the boundary equilibria of model (1).

Theorem 4.

- (i) If $c > \mu$ and $r < d$, the tumor-free equilibrium F_1 of model (1) is globally asymptotically stable for any time delay $\tau \geq 0$.
- (ii) If $c > \mu$ and $r = d$, the tumor-free equilibrium F_1 of model (1) is globally attractive for any time delay $\tau \geq 0$.

Proof. First, for any solution $(T(t), P(t), E(t))$ of model (1), from $\dot{E}(t) \geq E(t)(c - \mu - bcE(t))$, we easily have that $\liminf_{t \rightarrow +\infty} E(t) \geq (c - \mu)/(bc) = \bar{E}$. Define

$$G_1 = \{ \phi = (\phi_1, \phi_2, \phi_3) \in G \mid 0 \leq \phi_1 \leq T_M, 0 \leq \phi_2 \leq P_M, \bar{E} \leq \phi_3 \leq E_M \}.$$

From Theorem 1, we see that G_1 attracts all solutions of model (1). For any $\phi = (\phi_1, \phi_2, \phi_3) \in G_1$, let $(T(t), P(t), E(t))$ be the solution of model (1) with the initial function ϕ . Clearly, for any $t \geq 0$, we have that $E(t) > 0$. We claim that for any $t \geq 0$, $E(t) \geq \bar{E}$. In fact, if there is $t_1 > 0$ such that $E(t_1) < \bar{E}$, then $E(t) < \bar{E}$ for $t_2 < t \leq t_1$, here $t_2 = \sup\{t \mid E(t) = \bar{E}, t \leq t_1\} \geq 0$. From Lagrange mean value theorem, there exists some $\xi \in (t_2, t_1)$ such that $0 < E(\xi) < \bar{E}$ and $\dot{E}(\xi) < 0$. Hence, we have that

$$\dot{E}(\xi) = bcE(\xi)(\bar{E} - E(\xi)) + \frac{\beta E(\xi)P(\xi)}{g + P(\xi)} > 0.$$

This is a contradiction to $\dot{E}(t_1) < 0$. Hence, G_1 is positively invariant with respect to model (1).

To prove global stability of F_1 , let us define a functional L on G_1 as follows:

$$L(\phi_1, \phi_2, \phi_3) = \phi_1(0).$$

Calculating the time derivative of L along solutions of model (1), we obtain

$$\dot{L}(\phi)|_{(1)} = (r - d)\phi_1(0) - \frac{r\phi_1^2(0)}{k + \Gamma\phi_3(0)}.$$

By $r \leq d$, we have that

$$\dot{L}(\phi)|_{(1)} \leq -\frac{r\phi_1^2(0)}{k + \Gamma\phi_3(0)} \leq 0 \tag{12}$$

for any $\phi \in G_1$. This show that $L(\phi)$ is a Liapunov function on the subset G_1 in C .

Define $D = \{\phi \in G_1 \mid \dot{L}(\phi)|_{(1)} = 0\}$. From (12), we have that

$$D \subset \{\phi \in G_1 \mid \phi_1(0) = 0\}.$$

Let M be the largest set in D , which is invariant with respect to model (1). Clearly, M is not empty since $(0, 0, (c - \mu)/(bc)) \in M$. For any $\phi \in M$, let $(T(t), P(t), E(t))$ be the solution of model (1) with the initial function ϕ . From the invariance of M , we have that $(T_t, P_t, E_t) \in M \subset D$ for any $t \in \mathbb{R}$. Thus, $T(t) \equiv 0$ for any $t \in \mathbb{R}$. If $P(0) > 0$, from the second equation of model (1), we have that $P(t) \rightarrow +\infty$ as $t \rightarrow -\infty$. This is a contradiction to boundedness of G_1 . Hence, the invariance of M implies $P(t) \equiv 0$ for any $t \in \mathbb{R}$. From the third equation of model (1), we have that $E(t) \rightarrow (c - \mu)/(bc) = \bar{E}$ as $t \rightarrow +\infty$. Hence, the invariance of M implies that $E(t) \equiv \bar{E}$ for any $t \in \mathbb{R}$. Therefore, $M = \{(0, 0, \bar{E})\}$. The classical Liapunov–LaSalle invariance principal (see, for example, [14]) shows that F_1 is globally attractive. Since it has been shown that, if $r < d$ and $c > \mu$, F_1 is locally asymptotically stable for any time delay $\tau \geq 0$. Hence, if $c > \mu$ and $r < d$, F_1 is globally asymptotically stable for any time delay $\tau \geq 0$. If $c > \mu$ and $r = d$, F_1 is globally attractive for any time delay $\tau \geq 0$.

This completes the proof. □

Theorem 5. *If $r > d$ and $c - \mu + \beta \leq 0$, the endothelium-free equilibrium F_2 of model (1) is globally asymptotically stable for any time delay $\tau \geq 0$.*

Proof. For any solution $(T(t), P(t), E(t))$ of model (1), from $\dot{T}(t) \geq T(t)(r - d - rT(t)/k)$, we easily have that $\liminf_{t \rightarrow +\infty} T(t) \geq k(r - d)/r = \hat{T}$. Define

$$G_2 = \left\{ \phi = (\phi_1, \phi_2, \phi_3) \in C \mid \hat{T} \leq \phi_1 \leq T_M, \right. \\ \left. 0 \leq \phi_2 \leq P_M, 0 \leq \phi_3 \leq E_M \right\}.$$

We see that G_2 attracts all solutions of model (1). For any $\phi = (\phi_1, \phi_2, \phi_3) \in G_2$, let $(T(t), P(t), E(t))$ be the solution of model (1) with the initial function ϕ . By similar method as in the proof of Theorem 4, we can show that G_2 is positively invariant with respect to model (1).

To prove global stability of F_2 , let us define a functional W on G_2 as follows:

$$W(\phi_1, \phi_2, \phi_3) = \phi_3(0).$$

Calculating the time derivative of W along solutions of model (1), we obtain

$$\begin{aligned} \dot{W}(\phi)|_{(1)} &= c\phi_3(0)(1 - b\phi_3(0)) + \frac{\beta\phi_3(0)\phi_2(0)}{g + \phi_2(0)} - \mu\phi_3(0) \\ &\leq \phi_3(0)(c - \mu + \beta - bc\phi_3(0)). \end{aligned}$$

By $c - \mu + \beta \leq 0$, we have that

$$\dot{W}(\phi)|_{(1)} \leq -bc\phi_3^2(0) \leq 0 \tag{13}$$

for any $\phi \in G_2$. This show that $\widehat{W}(\phi)$ is a Liapunov function on the subset G_2 in C .

Define $D = \{\phi \in G_2 \mid \dot{W}(\phi)|_{(1)} = 0\}$. From (13), we have that

$$D \subset \{\phi \in G_2 \mid \phi_3(0) = 0\}.$$

Let M be the largest set in D , which is invariant with respect to model (1). Clearly, M is not empty since $(k(r - d)/r, \alpha k(r - d)/(rh), 0) \in M$. For any $\phi \in M$, let $(T(t), P(t), E(t))$ be the solution of model(1) with the initial function ϕ . From the invariance of M , we have that $(T_t, P_t, E_t) \in M \subset D$ for any $t \in \mathbb{R}$. Thus, $E(t) \equiv 0$ for any $t \in \mathbb{R}$. From the first equation of model (1) and $E(t) \equiv 0$ for any $t \in \mathbb{R}$, we further have that $T(t) \rightarrow k(r - d)/r = \widehat{T}$ as $t \rightarrow +\infty$. Hence, the invariance of M implies that $T(t) \equiv \widehat{T}$ for any $t \in \mathbb{R}$. From the second equation of model(1), we have that $\dot{P}(t) = \alpha\widehat{T} - hP(t)$ for any $t \in \mathbb{R}$. If $P(0) \neq \widehat{P}$, it has that $|P(t)| = |(P(0) - \widehat{P})e^{-ht} + \widehat{P}| \rightarrow +\infty$ as $t \rightarrow -\infty$. This is a contradiction to boundedness of G_2 . Hence, the invariance of M implies that $P(t) \equiv \widehat{P}$ for any $t \in \mathbb{R}$. Therefore, $M = \{(\widehat{T}, \widehat{P}, 0)\}$. The classical Liapunov–LaSalle invariance principal (see, for example, [14]) shows that F_2 is globally attractive. Since it has been shown that, if $r > d$ and $c - \mu + \beta < 0$, F_2 is locally asymptotically stable for any time delay $\tau \geq 0$. Hence, F_2 is globally asymptotically stable for any time delay $\tau \geq 0$.

This completes the proof. □

4.2 Global stability of the angiogenesis equilibrium

In this section, we study the global stability of the angiogenesis equilibrium of model (1) in G .

Theorem 6. *If $r > d$ and $c \geq \mu$ hold, the angiogenesis equilibrium $F^* = (T^*, P^*, E^*)$ of model (1) is globally asymptotically stable provided that $A_1 > 0$, $A_2 > 0$ and $A_3 > 0$, where*

$$\begin{aligned} A_1 &= \frac{r}{k + \Gamma E_M} - \frac{r\Gamma T^*}{2k(k + \Gamma E^*)} - \frac{\alpha}{2} - \frac{\alpha r \tau T_M}{2k} > 0, \\ A_2 &= h - \frac{\alpha}{2} - \frac{\beta}{2(g + P^*)} - \frac{\alpha \tau r T_M (k + \Gamma E^* + \Gamma T^*)}{2k(k + \Gamma E^*)} > 0, \\ A_3 &= bc - \frac{r\Gamma T^* (2\alpha \tau T_M + 1)}{2k(k + \Gamma E^*)} - \frac{\beta}{2(g + P^*)} > 0. \end{aligned} \tag{14}$$

Proof. Let $(T(t), P(t), E(t))$ be any positive solution of model (1) with initial conditions (2).

Define

$$V_1 = T - T^* - T^* \ln \frac{T}{T^*} + \frac{1}{2}(P - P^*)^2 + E - E^* - E^* \ln \frac{E}{E^*}.$$

Calculating the derivative of V_1 along positive solution of model (1), it follows that

$$\begin{aligned} \frac{dV_1}{dt} &= \left(1 - \frac{T^*}{T(t)}\right) \left(rT(t)\left(1 - \frac{T(t)}{k + \Gamma E(t)}\right) - dT(t)\right) \\ &\quad + (P(t) - P^*)(\alpha T(t - \tau) - hP(t)) \\ &\quad + \left(1 - \frac{E^*}{E(t)}\right) \left(cE(t)(1 - bE(t)) + \frac{\beta E(t)P(t)}{g + P(t)} - \mu E(t)\right). \end{aligned} \tag{15}$$

Equation (15) can be rewritten as

$$\begin{aligned} \frac{dV_1}{dt} &= \left(r - d - \frac{rT(t)}{k + \Gamma E(t)}\right) (T(t) - T^*) \\ &\quad + (P(t) - P^*)(\alpha(T(t - \tau) - T^*) - h(P(t) - P^*)) \\ &\quad + \left(c(1 - bE(t)) + \frac{\beta P(t)}{g + P(t)} - \mu\right) (E(t) - E^*). \end{aligned} \tag{16}$$

Substituting $r - d = rT^*/(k + \Gamma E^*)$ and $c - \mu = bcE^* - \beta P^*/(g + P^*)$ into (16), we obtain that

$$\begin{aligned} \frac{dV_1}{dt} &= \left(\frac{rT^*}{k + \Gamma E^*} - \frac{rT(t)}{k + \Gamma E(t)}\right) (T(t) - T^*) \\ &\quad + (P(t) - P^*)(\alpha(T(t - \tau) - T^*) - h(P(t) - P^*)) \\ &\quad + \left(bcE^* - \frac{\beta P^*}{g + P^*} - bcE(t) + \frac{\beta P(t)}{g + P(t)}\right) (E(t) - E^*) \\ &= -\frac{r}{(k + \Gamma E(t))} (T(t) - T^*)^2 \\ &\quad + \frac{r\Gamma T^*}{(k + \Gamma E(t))(k + \Gamma E^*)} (T(t) - T^*)(E(t) - E^*) \\ &\quad + (P(t) - P^*) \left(\alpha(T(t) - T^*) - h(P(t) - P^*) - \alpha \int_{t-\tau}^t T(u) du\right) \\ &\quad - bc(E(t) - E^*)^2 + \frac{\beta g}{(g + P^*)(g + P(t))} (P(t) - P^*)(E(t) - E^*). \end{aligned} \tag{17}$$

Substituting $\dot{T}(u)$ into (17), we obtain that

$$\begin{aligned} \frac{dV_1}{dt} = & -\frac{r}{(k + \Gamma E(t))} (T(t) - T^*)^2 \\ & + \frac{r\Gamma T^*}{(k + \Gamma E(t))(k + \Gamma E^*)} (T(t) - T^*) (E(t) - E^*) \\ & + \alpha (T(t) - T^*) (P(t) - P^*) - h (P(t) - P^*)^2 \\ & - \alpha (P(t) - P^*) \int_{t-\tau}^t T(u) \left(-\frac{r(T(u) - T^*)}{k + \Gamma E(u)} + \frac{r\Gamma T^*(E(u) - E^*)}{(k + \Gamma E^*)(k + \Gamma E(u))} \right) du \\ & - bc (E(t) - E^*)^2 + \frac{\beta g}{(g + P^*)(g + P(t))} (P(t) - P^*) (E(t) - E^*). \end{aligned} \quad (18)$$

From equation (18) and by using the inequality $a^2 + b^2 \geq 2ab$, we obtain that

$$\begin{aligned} \frac{dV_1}{dt} \leq & \left(-\frac{r}{(k + \Gamma E(t))} + \frac{r\Gamma T^*}{2(k + \Gamma E(t))(k + \Gamma E^*)} + \frac{\alpha}{2} \right) (T(t) - T^*)^2 \\ & + \left(-h + \frac{\alpha}{2} + \frac{\beta g}{2(g + P^*)(g + P(t))} \right) (P(t) - P^*)^2 \\ & + \left(-bc + \frac{r\Gamma T^*}{2(k + \Gamma E(t))(k + \Gamma E^*)} + \frac{\beta g}{2(g + P^*)(g + P(t))} \right) (E(t) - E^*)^2 \\ & + \frac{\alpha}{2} (P(t) - P^*)^2 \int_{t-\tau}^t T(u) \left(\frac{r}{k + \Gamma E(u)} + \frac{r\Gamma T^*}{(k + \Gamma E(u))(k + \Gamma E^*)} \right) du \\ & + \frac{\alpha}{2} \int_{t-\tau}^t T(u) \left(\frac{r(T(u) - T^*)^2}{k + \Gamma E(u)} + \frac{r\Gamma T^*(E(u) - E^*)^2}{(k + \Gamma E(u))(k + \Gamma E^*)} \right) du. \end{aligned} \quad (19)$$

From (19), we obtain that

$$\begin{aligned} \frac{dV_1}{dt} \leq & \left(-\frac{r}{(k + \Gamma E(t))} + \frac{r\Gamma T^*}{2(k + \Gamma E(t))(k + \Gamma E^*)} + \frac{\alpha}{2} \right) (T(t) - T^*)^2 \\ & + \left(-h + \frac{\alpha}{2} + \frac{\beta g}{2(g + P^*)(g + P(t))} \right) (P(t) - P^*)^2 \\ & + \left(-bc + \frac{r\Gamma T^*}{2(k + \Gamma E(t))(k + \Gamma E^*)} + \frac{\beta g}{2(g + P^*)(g + P(t))} \right) (E(t) - E^*)^2 \\ & + \frac{\alpha T_M}{2} (P(t) - P^*)^2 \int_{t-\tau}^t \left(\frac{r}{k + \Gamma E(u)} + \frac{r\Gamma T^*}{(k + \Gamma E(u))(k + \Gamma E^*)} \right) du \\ & + \frac{\alpha T_M}{2} \int_{t-\tau}^t \left(\frac{r(T(u) - T^*)^2}{k + \Gamma E(u)} + \frac{r\Gamma T^*(E(u) - E^*)^2}{(k + \Gamma E(u))(k + \Gamma E^*)} \right) du. \end{aligned} \quad (20)$$

By (20), we get that

$$\begin{aligned} \frac{dV_1}{dt} \leq & \left(-\frac{r}{(k + \Gamma E_M)} + \frac{r\Gamma T^*}{2k(k + \Gamma E^*)} + \frac{\alpha}{2} \right) (T(t) - T^*)^2 \\ & + \left(-h + \frac{\alpha}{2} + \frac{\beta}{2(g + P^*)} + \frac{\alpha T_M \tau r (k + \Gamma E^* + \Gamma T^*)}{2k(k + \Gamma E^*)} \right) (P(t) - P^*)^2 \\ & + \left(-bc + \frac{r\Gamma T^*}{2k(k + \Gamma E^*)} + \frac{\beta}{2(g + P^*)} \right) (E(t) - E^*)^2 \\ & + \frac{\alpha}{2} T_M \int_{t-\tau}^t \left(\frac{r}{k} (T(u) - T^*)^2 + \frac{r\Gamma T^*}{k(k + \Gamma E^*)} (E(u) - E^*)^2 \right) du. \end{aligned} \tag{21}$$

Define

$$\begin{aligned} V_2 = & \frac{\alpha T_M r}{2k} \int_{t-\tau}^t \int_s^t (T(u) - T^*)^2 du ds \\ & + \frac{\alpha T_M r \Gamma T^*}{2k(k + \Gamma E^*)} \int_{t-\tau}^t \int_s^t (E(u) - E^*)^2 du ds. \end{aligned} \tag{22}$$

It follows from (21) and (22) that

$$\frac{dV_1}{dt} + \frac{dV_2}{dt} \leq -A_1(T(t) - T^*)^2 - A_2(P(t) - P^*)^2 - A_3(E(t) - E^*)^2,$$

where A_1, A_2 and A_3 are defined by (14).

Therefore, equation (14) ensures that $dV_1/dt + dV_2/dt \leq 0$, and $dV_1/dt + dV_2/dt = 0$ if and only if $T = T^*, P = P^*$ and $E = E^*$. It is easy to know that $F^* = (T^*, P^*, E^*)$ is the largest invariant set in $D = \{(T, P, E) \in G \mid (dV_1/dt + dV_2/dt)|_{(1)} = 0\}$. From the Liapunov–LaSalle invariance principal (see, for example, [14]) shows that F^* is globally asymptotically stable if $A_1 > 0, A_2 > 0$ and $A_3 > 0$.

This completes the proof. □

We summarize the stability results (LAS and GAS) in the following table.

Table 1. The stability results.

Equilibrium	The conditions of locally asymptotically stable	The conditions of globally asymptotically stable
F_0	$r < d, c < \mu$	$r < d, c < \mu$
F_1	$r < d, c > \mu$	$r < d, c > \mu$
F_2	$r > d,$ $\alpha k(r - d)(c - \mu + \beta) + grh(c - \mu) < 0$	$r > d, c - \mu + \beta \leq 0$
F^*	$r > d, c \geq \mu$	$r > d, c \geq \mu,$ $A_1 > 0, A_2 > 0, A_3 > 0$

5 Discussion and numerical simulations

In this paper, we explore the effects and interactions of cancer cells, angiogenic factors and endothelial cells via a system of nonlinear delay differential equations. We take into account the angiogenic growth factors secreted by the tumor associated with the angiogenic process, which helps the tumor growth. We investigate the stability properties of all the equilibria of model (1). Our results show that the time delay is actually harmless for local and global dynamical properties of model (1).

Next, we carry out some numerical simulations of model (1) to illustrate the theoretical results obtained in Section 3. Parameter values used for numerical simulations are given in Table 2.

Next, we present numerical simulations. From Theorem 2(i), we know that, for smaller growth rate r of tumor cells and smaller proliferation rate c of endothelial cells, the tumor cells, angiogenic promoters and the endothelial cells can be eventually eliminated (see Fig. 2). Condition (ii) in Theorem 2 imply that for a very low growth rate of tumor cells

Table 2. Parameter values used in the numerical simulations.

Description	Parameter	Value
Cancer cells proliferation rate	r	Varies
The endothelial cells proliferation rate	c	Varies
Carrying capacity of cancer cells	k	195
Carrying capacity of the endothelial cells	$1/b$	1/210
Proportion of the endothelial cells due to angiogenesis	Γ	0.15
The rate of the angiogenic promoters produced by cancer cells	α	0.000371
The rate of the endothelial cells growth	β	0.1245
The half saturation constant of the endothelial cells	g	2×10^7
The mortality of cancer cells	d	Varies
The mortality of angiogenic promoters	h	0.1 day^{-1}
The mortality of the endothelial cells	μ	Varies

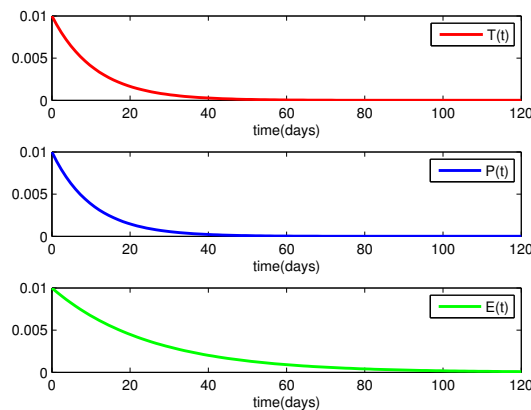


Figure 2. The equilibrium $F_0 = (0, 0, 0)$ of model (1) is locally asymptotically stable when $r = 0.01$, $d = 0.1$, $c = 0.01$, $\mu = 0.05$, $\tau = 1$ and other values are shown in Table 2. The initial functions are $(0.01, 0.01, 0.01)$.

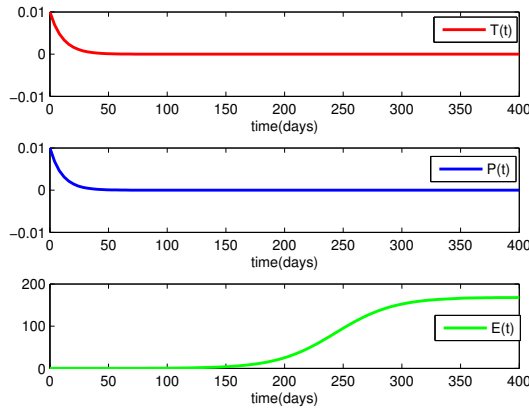


Figure 3. The equilibrium $F_1 = (0, 0, 168)$ of model (1) is locally asymptotically stable when $r = 0.01$, $d = 0.1$, $c = 0.05$, $\mu = 0.01$, $\tau = 1$ and other values are shown in Table 2. The initial functions are $(0.01, 0.01, 0.01)$.

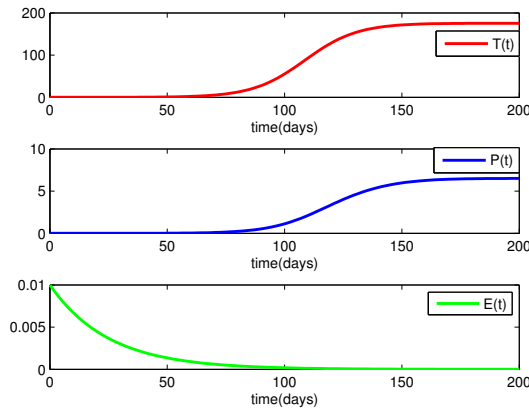


Figure 4. The equilibrium $F_2 = (175.5, 6.51, 0)$ of model (1) is locally asymptotically stable when $r = 0.1$, $d = 0.01$, $c = 0.01$, $\mu = 0.05$, $\tau = 1$ and other values are shown in Table 2. The initial functions are $(0.01, 0.01, 0.01)$.

and high proliferation rate of endothelial cells, the endothelial cells can not be eliminated (see Fig. 3). From Theorem 2(iii), we know that, for higher growth rate of tumor cells, smaller proliferation and growth rates of endothelial cells, the endothelial cells will not be stimulated by angiogenic growth factors that are produced by cancer cells (see Fig. 4).

For model (1), let us choose the parameter values as follows, $r = 0.1$, $c = 0.2$, $d = 0.01$, $\mu = 0.01$. The other parameters values are shown in Table 2. From Theorem 3, we know that the angiogenesis equilibrium F^* is locally asymptotically stable for all $\tau \geq 0$ (see Fig. 5). Next, we choose the parameter values as follows, $r = 0.1$, $d = 0.01$, $c = 0.1$, $\mu = 0.2$, $g = 20$, $\Gamma = 1000$, $\tau = 1$ and other parameters values are shown in Table 2. By simple computations, we can obtain two angiogenesis equilibria

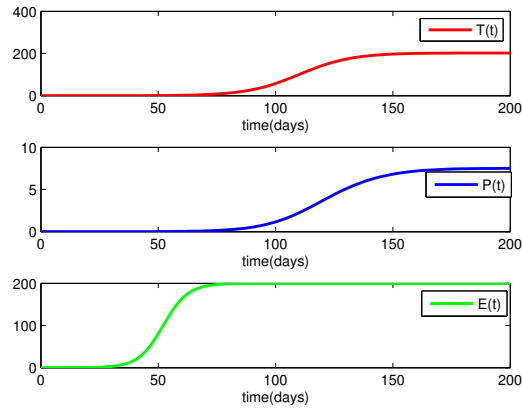


Figure 5. The equilibrium $F^* = (202.4325, 7.5102, 199.5)$ of model (1) is locally asymptotically stable when $r = 0.1$, $d = 0.01$, $c = 0.2$, $\mu = 0.01$, $\tau = 1$ and other values are shown in Table 2. The initial functions are $(0.01, 0.01, 0.01)$.

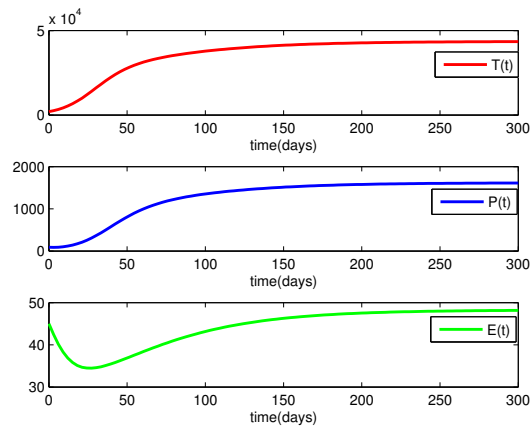


Figure 6. The equilibrium $F^* = (43880, 1627.9, 45.44)$ of model (1) is locally asymptotically stable when $r = 0.1$, $d = 0.01$, $c = 0.1$, $\mu = 0.2$, $g = 20$, $\Gamma = 1000$, $\tau = 1$ and other values are shown in Table 2. The initial functions are $(2000, 90, 45)$.

$F^* = (43880, 1627.9, 45.44)$ and $F^{**} = (2320.3, 86.08, 45.44)$. Figure 6 shows that the angiogenesis equilibrium $F^* = (43880, 1627.9, 45.44)$ is locally asymptotically stable for all $\tau \geq 0$.

It would be interesting to consider more general models with immune responses. Such modifications should be more reasonable in reality and give us more insights into the cancer therapies, but some complicated dynamic behaviors may occur, such as periodic oscillations and back-ward bifurcations etc. We leave this as a future work.

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