DOI:10.13878/j.cnki.jnuist.2017.04.004

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一类三次超越多项式零点的分布及其在时滞生物系统的应用

摘要

本文讨论了一类三次超越多项式零点的分布,给出了零点分布在左半复平面、穿过虚轴和进入右半复平面的充分条件.作为应用,考虑了带时滞的三种群食物链模型、带时滞的睾酮分泌模型、带时滞的 HIV 体内感染动力学模型、带时滞的葡萄糖-胰岛素模型、带时滞的肿瘤-免疫系统作用模型的稳定性和分支问题.

关键词

时滞微分方程;稳定性;分支;超越方程;生物系统

中图分类号 O175.1

文献标志码 A

收稿日期 2016-04-18

资助项目 美国 NSF 基金(DMS-1412454);国家自然科学基金(11371248)

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0　导读

本文原文为英文,希望感兴趣的读者进一步关注原文.

由于物理、生物、医学等状态在现时刻的变化率通常依赖于过去,应用科学中的很多实际问题要用时滞微分方程来描述.时滞微分方程的平衡点被称为是绝对稳定的如果对于所有时滞取值它是稳定的;平衡点被称为是条件稳定的如果对于某些时滞取值它是稳定的.而时滞微分方程平衡点的稳定性由其线性化系统的特征方程确定:平衡点是稳定的如果其特征方程的所有根都具有负实部;如果其特征方程至少有一个根具有正实部,则平衡点是不稳定的.时滞微分方程的平衡点对应的特征方程含有指数项,属于超越函数方程,可能具有无穷多个根.因此,研究超越多项式方程根在复平面上的分布对讨论时滞微分方程的稳定性和分支非常重要.

三维时滞微分方程组的特征方程是一个三次超越多项式方程.我们考虑如下一类三次超越多项式方程:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 + (b_1\lambda^2 + b_2\lambda + b_3)e^{-\lambda\tau} = 0$$

的根在复平面上的分布,给出了三次超越多项式零点分布在左半复平面、穿过虚轴和进入右半复平面的充分条件.基本思想和技巧是首先假设当 $\tau = 0$ 时,对应的三次多项式方程的所有根具有负实部;根据连续性,当 $\tau > 0$ 充分小时三次超越多项式方程的所有根仍然具有负实部;如果对所有的 $\tau > 0$ 方程的所有根具有负实部,则相应的绝对稳定性可以得到;如果特征根的实部随着 τ 的增加从负值增到零,即存在 $\tau_0>0$ 在使得 $\mathrm{Re}\lambda(\tau_0) = 0$,且横截条件 $\frac{\mathrm{d}}{\mathrm{d}\tau}\mathrm{Re}\lambda(\tau_0) > 0$ 成立,则对应的模型平衡点当 $\tau < \tau_0$ 时是稳定的,当 $\tau > \tau_0$ 时是不稳定的,当 $\tau = \tau_0$ 时 Hopf 分支发生.

作为应用,我们将所得结果用于讨论带时滞的三种群食物链模型、带时滞的睾酮分泌模型、带时滞的 HIV 体内感染动力学模型、带时滞的葡萄糖-胰岛素模型、带时滞的肿瘤-免疫系统作用模型等,考虑了这些生物和医学模型的稳定性和分支问题.类似的方法可以用来讨论具有两个指数项的三次超越多项式方程根在复平面上的分布以及带两个时滞的三维微分方程模型的稳定性和分支问题.

On the distribution of zeros of a third-degree exponential polynomial with applications to delayed biological systems

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Abstract We consider the distribution of roots to a general third-order exponential polynomial equation and give detailed conditions about when all roots lie on the left half plane, a pair of roots cross the imaginary axis and enter the right half plane. These results can be used to discuss the local stability and Hopf bifurcation of three-dimensional biological systems with delay. We apply our results to the three-species delayed food chain models, delayed models for the control of testosterone secretion, delayed models of within-host HIV infection of CD4+T-cells, glucose-insulin systems with delay, and tumor-immune system interaction models with delay.

Key words delayed differential equations; stability; bifurcation; transcendental equation; biological systems

0 Introduction

In order to study the nonlinear dynamics of a delayed differential system, it is crucial to discuss the distribution of zeros of the (transcendental) exponential polynomial associated to the characteristic equation of the linearized system at a given equilibrium (Bellman and Cooke[1]). An equilibrium of a delayed differential system is absolutely stable if all roots of the corresponding exponential polynomial equation have negative real parts for all delay values; it is conditionally stable if all roots of the corresponding exponential polynomial equation have negative real parts for some delay values; and it is unstable if at least one root of the corresponding exponential polynomial equation has positive real part for any positive delay value.

The distribution of roots to general exponential polynomial equations has been extensively studied in the literature, see, for example, Avellar and Hale[2], Baptistini and Táboas[3], Bellman and Cooke[1], Brauer[4], Chin[5], Cooke and Grossman[6], Cooke and van den Driessche[7], Hale and Verduyn Lunel[8], Hayes[9], Liao[10], Ruan and Wei[11], and the references cited therein. Consider the following nth-order exponential polynomial

$$\begin{aligned}P(\lambda,e^{-\lambda\tau_1},\cdots,e^{-\lambda\tau_m})=&\\ \lambda^n+p_1^{(0)}\lambda^{n-1}+\cdots+p_{n-1}^{(0)}\lambda+p_n^{(0)}+&\\ [p_1^{(1)}\lambda^{n-1}+\cdots+p_{n-1}^{(1)}\lambda+p_n^{(1)}]e^{-\lambda\tau_1}+\cdots+&\\ [p_1^{(m)}\lambda^{n-1}+\cdots+p_{n-1}^{(m)}\lambda+p_n^{(m)}]e^{-\lambda\tau_m},&\qquad(1)\end{aligned}$$

where $\tau_i\geqslant 0\,(i=1,2,\cdots,m)$ and $p_j^{(i)}\,(i=0,1,\cdots,m;\ j=1,2,\cdots,n)$ are constants. The following result was proved in[11].

Lemma 1 As $(\tau_1,\tau_2,\cdots,\tau_m)$ vary, the sum of the orders of the zeros of $P(\lambda,e^{-\lambda\tau_1},\cdots,e^{-\lambda\tau_m})$ in the open right half plane can change only if a zero appears on or crosses the imaginary axis.

In this paper, we first apply Lemma 1 to study the distribution of roots to the following third-degree exponential polynomial equation

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3+(b_1\lambda^2+b_2\lambda+b_3)e^{-\lambda\tau}=0.\qquad(2)$$

Then we apply the results to discuss the stability and bifurcation of several three-dimensional biological systems with delay.

Notice that if $\tau=0$, equation (2) reduces to the third-order polynomial equation

$$\lambda^3+(a_1+b_1)\lambda^2+(a_2+b_2)\lambda+(a_3+b_3)=0.\qquad(3)$$

1 Distribution of zeros of the third-degree exponential polynomial

By the Routh-Hurwitz criterion, it follows that all eigenvalues of equation (3) have negative real parts if and only if

$$a_1+b_1>0,\ a_3+b_3>0,\ (a_1+b_1)(a_2+b_2)-(a_3+b_3)>0.\qquad(4)$$

Let $\lambda(\tau)=\alpha(\tau)\pm i\omega(\tau)$ denote the roots of the third-order exponential polynomial equation (2).

Firstly, we assume that the conditions in (4) are satisfied so that all roots of the third-order exponential polynomial equation (2) when $\tau=0$ (that is equation (3) have negative real parts, $\alpha(0)<0$). By continuity, if $\tau>0$ is sufficiently small we still have $\alpha(\tau)<0$. Now we consider three possibilities: (ⅰ) $\alpha(\tau)<0$ for all values of τ (so that all roots lie on the left half plane); (ⅱ) $\alpha(\tau_0)=0$ for certain value $\tau_0>0$ (so that the roots appear on the imaginary axis, i.e., $\pm i\omega(\tau_0)$ are purely imaginary roots); (ⅲ) $\pm i\omega(\tau_0)$ for $\tau\geqslant\tau_0$ (so that the roots cross the imaginary axis and enter the right half plane).

Note that if $i\omega(\omega>0)$ is a root of equation (2) if and only if

$$-i\omega^3-a_1\omega^2+ia_2\omega+a_3+(-b_1\omega^2+ib_2\omega+b_3)(\cos(\omega\tau)-i\sin(\omega\tau))=0. \quad (5)$$

Separating the real and imaginary parts, we have

$$a_1\omega^2-a_3=(-b_1\omega^2+b_3)\cos(\omega\tau)+b_2\omega\sin(\omega\tau),$$
$$\omega^3-a_2\omega=b_2\omega\cos(\omega\tau)-(-b_1\omega^2+b_3)\sin(\omega\tau). \quad (6)$$

Adding up the squares of both equations, we obtain

$$\omega^6+(a_1^2-b_1^2-2a_2)\omega^4+(a_2^2-b_2^2-2a_1a_3+2b_1b_3)\omega^2+(a_3^2-b_3^2)=0. \quad (7)$$

Let

$$z=\omega^2,\quad p=a_1^2-b_1^2-2a_2,$$
$$q=a_2^2-b_2^2-2a_1a_3+2b_1b_3,\quad r=a_3^2-b_3^2. \quad (8)$$

Then equation (7) becomes

$$h(z)=z^3+pz^2+qz+r=0. \quad (9)$$

Clearly, $h(0)=r<0$, and $\lim\limits_{z\to\infty}h(z)=\infty$. Hence, there exists a $z_0\in(0,\infty)$ so that $h(z_0)=0$, and we have the following lemma.

Lemma 2 If $r<0$, then equation (9) has at least one positive root.

Lemma 3 If $r\geqslant0$, then the necessary condition for equation (9) to have positive real roots is

$$p^2-3q\geqslant0. \quad (10)$$

Proof. From (9) we have

$$\frac{\mathrm{d}h(z)}{\mathrm{d}z}=3z^2+2pz+q.$$

Set

$$3z^2+2pz+q=0. \quad (11)$$

Then the roots of equation (11) can be expressed as

$$z_{1,2}=\frac{-p\pm\sqrt{p^2-3q}}{3}. \quad (12)$$

If $p^2-3q<0$, then (11) does not have real roots. So the function $h(z)$ is monotone increasing in z. It follows from $h(0)=r\geqslant0$ that equation (9) has no positive real roots. This completes the proof.

Clearly, if $p^2-3q\geqslant0$, then $z_1=\frac{-p+\sqrt{p^2-3q}}{3}$ is the local minimum of $h(z)$. Thus, we have the following lemma.

Lemma 4 If $r\geqslant0$, then equation (9) has positive roots if and only if $z_1>0$ and $h(z_1)\leqslant0$.

Proof. The sufficiency is obvious. We only need to prove the necessity. Otherwise, we assume that either $z_1\leqslant0$ or $z_1>0$ and $h(z_1)>0$. If $z_1\leqslant0$, since $h(z)$ is increasing for $z\geqslant z_1$ and $h(0)=r\geqslant0$, it follows that $h(z)$ has no positive real zeros. If $z_1>0$ and $h(z_1)>0$, since $z_2=\frac{-p-\sqrt{p^2-3q}}{3}$ is the local maximum value, it follows that $h(z_1)<h(z_2)$. Hence, by $h(0)=r\geqslant0$, we know that $h(z)$ does not have positive real zeros. This completes the proof.

Summarizing the above discussion, we have the following proposition.

Proposition 1 We have the following statements

(ⅰ) If $r<0$, then equation (9) has at least one positive root.

(ⅱ) If $r\geqslant0$ and $p^2-3q<0$, then equation (9) has no positive roots.

(ⅲ) If $r\geqslant0$, then equation (9) has positive roots if and only if $z_1=\frac{1}{3}(-p+\sqrt{p^2-3q})>0$ and $h(z_1)\leqslant0$.

Suppose that equation (9) has positive roots. Without loss of generality, we assume that it has three positive roots, denoted by z_1, z_2, and z_3, respectively. Then equation (7) has three positive roots, say

$$\omega_1=\sqrt{z_1},\omega_2=\sqrt{z_2},\omega_3=\sqrt{z_3}.$$

Let

$$\tau_k^{(j)}=\frac{1}{\omega_k}\left[\arcsin\left(\frac{\omega_k^3+a_1\omega_k^2-a_2\omega_k-a_3}{2b_2\omega_k}\right)+2(j-1)\pi\right],$$
$$k=1,2,3;\quad j=0,1,\cdots.$$

Then $\pm i\omega_k$ is a pair of purely imaginary roots of equation (2) with $\tau=\tau_k^{(j)}$, $k=1,2,3$; $j=0,1,\cdots$. Clearly,

$$\lim_{j\to\infty}\tau_k^{(j)}=\infty,\ k=1,2,3.$$

Thus, we can define

$$\tau_0=\tau_{k_0}^{(j_0)}=\min_{1\leqslant k\leqslant 3,j\geqslant 1}\{\tau_k^{(j)}\},\quad \omega_0=\omega_{k_0}. \tag{13}$$

Proposition 2 Suppose that the conditions in (4) are satisfied.

(a) If $r\geqslant 0$ and $p^2-3q<0$, then all roots of equation (2) have negative real parts for all $\tau\geqslant 0$.

(b) If $r<0$ or $r\geqslant 0$, $-p+\sqrt{p^2-3q}>0$ and $h\left(\frac{1}{3}(-p+\sqrt{p^2-3q})\right)<0$, then all roots of equation (2) have negative real parts when $\tau\in[0,\tau_0)$.

Proof. If $r\geqslant 0$ and $p^2-3q<0$, Proposition 1 (ii) shows that equation (2) has no roots with zero real part for all $\tau\geqslant 0$. When $r<0$ or $r\geqslant 0$, $z_1=\frac{1}{3}(-p+\sqrt{p^2-3q})>0$ and $h(z_1)\leqslant 0$, Proposition 1 (i) and (iii) imply that when $\tau\neq\tau_k^{(j)}$, $k=1,2,3$, $j\geqslant 1$, equation (2) has no roots with zero real part and τ_0 is the minimum value of τ so that equation (2) has purely imaginary roots. Applying 1, we obtain the conclusion.

Let $\lambda(\tau)=\alpha(\tau)+i\omega(\tau)$ be the root of equation (2) satisfying

$$\alpha(\tau_0)=0,\quad \omega(\tau_0)=\omega_0.$$

In order to guarantee that $\pm i\omega_0$ are simple purely imaginary roots of equation (2) with $\tau=\tau_0$ and $\lambda(\tau)$ satisfies the transversality condition, we assume that $h'(\omega_0^2)\neq 0$. Hence, we have the following lemma.

Lemma 5 Suppose that $h'(\omega_0^2)\neq 0$. If $\tau=\tau_0$, then $\pm i\omega_0$ are a pair of simple purely imaginary roots of equation (2). Moreover, if the conditions of Proposition 2 (b) are satisfied, then

$$\frac{\mathrm{d}\mathrm{Re}\lambda(\tau_0)}{\mathrm{d}\tau}>0.$$

Proof. One can show that $i\omega_0$ is simple. Differentiating both sides of equation (2) with respect to τ gives

$$\frac{\mathrm{d}\lambda(\tau)}{\mathrm{d}\tau}=\frac{\lambda(b_1\lambda^2+b_2\lambda+b_3)\mathrm{e}^{-\lambda\tau}}{3\lambda^2+2a_1\lambda+a_2+[2b_1\lambda+b_2-\tau(b_1\lambda^2+b_2\lambda+b_3)]\mathrm{e}^{-\lambda\tau}}. \tag{14}$$

Denote

$$\begin{aligned}\Delta=&[-3\omega_0^2+a_2+(\tau_0b_1\omega_0^2+b_2-\tau_0b_3)\cos(\omega_0\tau_0)+\\&(2b_1\omega_0-\tau_0b_2\omega_0)\sin(\omega_0\tau_0)]^2+\\&[2a_1\omega_0-(\tau_0b_1\omega_0^2+b_2-\tau_0b_3)\sin(\omega_0\tau_0)+\\&(2b_1\omega_0-\tau_0b_2\omega_0)\cos(\omega_0\tau_0)]^2.\end{aligned}$$

Letting $\tau=\tau_0$ (i.e., $\alpha(\tau_0)=0$, $\omega(\tau_0)=\omega_0$) in equation (14), separating the real and imaginary parts, and using equation (6) and the definition of $h(z)$, we obtain that

$$\left.\frac{\mathrm{d}\mathrm{Re}\lambda}{\mathrm{d}\tau}\right|_{\tau=\tau_0}=\frac{\omega_0^2}{\Delta}h'(\omega_0^2)\neq 0.$$

If $\frac{\mathrm{d}\mathrm{Re}\lambda}{\mathrm{d}\tau}<0$ for $\tau<\tau_0$ and close to τ_0, then equation (2) has a root $\lambda(\tau)=\alpha(\lambda)+i\omega(\lambda)$ satisfying $\alpha(\lambda)>0$, which contradicts Proposition 2. This completes the proof.

By Proposition 2 and Lemma 5, we have the following theorem.

Theorem 1 Let p,q,r be defined by (8) and let ω_0 and τ_0 be defined by (13). Suppose that the conditions in (4) are satisfied. Then

(i) If $r\geqslant 0$ and $p^2-3q<0$, then all roots of equation (2) have negative real parts for all $\tau\geqslant 0$.

(ii) If $r<0$ or $r\geqslant 0$, $-p+\sqrt{p^2-3q}>0$ and $h\left(\frac{1}{3}(-p+\sqrt{p^2-3q})\right)<0$, then all roots of equation (2) have negative real parts when $\tau\in[0,\tau_0)$.

(iii) If the conditions of (ii) are satisfied, $\tau=\tau_0$, and $h'(\omega_0^2)\neq 0$, then $\pm i\omega_0$ are a pair of simple purely imaginary roots of equation (2) and all other roots have negative real parts. Moreover, $\frac{\mathrm{d}}{\mathrm{d}\tau}\mathrm{Re}\lambda(\tau_0)>0$.

2 Applications to delayed biological systems

In this section we apply the results in the above section to discuss the stability and bifurcation in several delayed biological systems described by three differential equations.

2.1 Three-species food chain models with delay

Let $x(t)$, $y(t)$, and $z(t)$ denote the densities of the bottom prey, intermediate predator, and top predator populations at time t, respectively. It is assumed that the intermediate predator $y(t)$ predates on the bottom prey $x(t)$ and is predated by the top predator $z(t)$ as well. Consider the three-species food chain model with delay (Freedman and Ruan[12]):

$$\begin{aligned}\frac{dx}{dt}&=xg(x,K)-yp(x),\\ \frac{dy}{dt}&=y[-r+cp(x)]-zq(y),\\ \frac{dz}{dt}&=z[-s+dq(y(t-\tau))]\end{aligned}\tag{15}$$

With initial values $x(0)=x_0\geqslant 0, y(\theta)=\varphi(\theta)\geqslant 0, \theta\in[-\tau,0], z(0)=z_0\geqslant 0$, in which $\varphi(\theta)$ is continuous for $\theta\in[-\tau,0]$, $\tau\geqslant 0$ is a constant which may be regarded as a delay due to gestation. (ⅰ) $g(x,K)$ describes the growth rate of the prey in the absence of predation and satisfies the assumptions that for any $x>0$ and $K>0$, $g(0,K)>0, g(K,K)=0, g_x(x,K)\leqslant 0, g_x(K,K)<0, g_K(x,K)>0, g_{xK}(x,K)>0$. The Logistic growth $g(x,K)=r\left(1-\frac{x}{K}\right)$ is a prototype and satisfies all these assumptions. (ⅱ) $p(x)$ denotes the predator functional response of y on x and satisfies the assumption that $p(0)=0, p(x)>0, p'(x)>0$ *for* $x>0$. Holling-type functional responses functions satisfy these conditions. (ⅲ) $q(y)$ denotes the predator functional response of z on y and satisfies similar conditions as for $p(x)$.

Let $E^*=(x^*,y^*,z^*)$ denote an interior equilibrium of system (15). The linearized system at E^* takes the following form

$$\begin{aligned}\frac{dX}{dt}&=m_{11}X(t)+m_{12}Y(t),\\ \frac{dY}{dt}&=m_{21}X(t)+m_{22}Y(t)+m_{23}Z(t),\\ \frac{dZ}{dt}&=m_{32}Z(t-\tau),\end{aligned}\tag{16}$$

where

$$\begin{aligned}&m_{11}=g(x^*,K)+x^*g_x(x^*,K)-y^*p'(y^*),\\ &m_{12}=-p(x^*)<0,\quad m_{21}=cy^*p'(x^*)>0,\\ &m_{22}=cp(x^*)-[r+z^*q'(y^*)],\quad m_{23}=-q(y^*)<0,\\ &m_{32}=dz^*q'(y^*)>0.\end{aligned}$$

The characteristic equation of the linearized system (16) is

$$\lambda^3+a_1\lambda^2+a_2\lambda+(b_2\lambda+b_3)e^{-\lambda\tau}=0,\tag{17}$$

where

$$\begin{aligned}&a_1=-(m_{11}+m_{22}),\quad a_2=m_{11}m_{22}-m_{12}m_{21},\\ &b_2=m_{23}m_{32}<0,\quad b_3=-m_{11}m_{23}m_{32}.\end{aligned}$$

One can verify that all conditions in (4) are satisfied if $m_{11}<0, m_{22}\leqslant 0$. Let p, q, r be defined by (8) with $a_3=b_1=0$ and let ω_0 and τ_0 be defined by (13). Then by Theorem 1, we have the following results.

Proposition 3 Assume that $m_{11}<0, m_{22}\leqslant 0$. Then the positive equilibrium E^* of system (15) is asymptotically stable if $\tau\in[0,\tau_0)$ and unstable if $\tau>\tau_0$. A Hopf biurcation occurs at E^* when $\tau=\tau_0$.

Remark 1 If a time delay appears in the growth term of the bottom prey, i.e., $g(x(t-\tau),K)$, or in the functional specific growth term of the intermediate predator, i.e., $p(x(t-\tau))$, then similar results on the stability and bifurcation of the model can be established.

2.2 Delayed models for the control of testosterone secretion

The secretion of testosterone from the gonads is stimulated by a pituitary hormone called the luteinizing hormone (LH). The secretion of LH from the pituitary gland is stimulated by the luteinizing hormone releasing hormone (LHRH). This LHRH is normally secreted by the hypothalamus and carried to the pituitary gland by the blood. It is known that testosterone (T) has a feedback effect on the secretion of LH and LHRH. It is believed that each of the hormones to be cleared from the bloodstream according to first order kinetics with LH and T produced by their precursors according to first order kinetics. There is a nonlinear negative feedback by T on LHRH and there is a delay between production of the hormones at one level and its effect on the production of the hormone it stimulates simply because of their spatial separation and the fact that the hormones are transported by circulating blood. Smith[13] proposed a delayed model involving the three hormones of LHRH, LH and T and a single delay indicating that the production of testosterone is delayed:

$$\begin{aligned}\frac{dR}{dt}&=f(T)-b_1(R),\\ \frac{dL}{dt}&=g_1(R)-b_2(L),\\ \frac{dT}{dt}&=g_2(L(t-\tau))-b_3(T),\end{aligned}\tag{18}$$

where f is a positive monotonic decreasing function, $b_i(i=1,2,3)$ *and* $g_j(j=1,2)$ are positive monotonic increasing functions, and τ is the delay associated with

the blood circulation time in the body, i.e., the time that LH requires to travel through the bloodstream to reach its site of action at the gonads.

Let $E^*=(R^*,L^*,T^*)$ denote the positive steady state of system (18). Then the linearized system of (18) at E^* is

$$\begin{aligned}\frac{dX}{dt}&=-b_{1'}(R^*)X+f'(T^*)Z,\\ \frac{dY}{dt}&=g_{1'}(R^*)X-b_{2'}(L^*)Y,\\ \frac{dZ}{dt}&=g_{2'}(L^*)Y(t-\tau)-b_{3'}(T^*)Z.\end{aligned}\tag{19}$$

The associated characteristic equation of system (19) is

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3+b_3e^{-\lambda\tau}=0,\tag{20}$$

where

$$\begin{aligned}a_1&=b_{1'}(R^*)+b_{2'}(L^*)+b_{3'}(T^*)>0,\\ a_2&=b_{1'}(R^*)b_{2'}(L^*)+b_{2'}(L^*)b_{3'}(T^*)+\\ &\quad b_{1'}(R^*)b_{3'}(T^*)>0,\\ a_3&=b_{1'}(R^*)b_{2'}(L^*)b_{3'}(T^*)>0,\\ b_3&=-f'(T^*)g_{1'}(R^*)g_{2'}(L^*)>0.\end{aligned}$$

We have

$$\begin{aligned}p&=a_1^2-2a_2=[b_{1'}(R^*)]^2+[b_{2'}(L^*)]^2+[b_{3'}(T^*)]^2,\\ q&=a_2^2-2a_1a_3=[b_{1'}(R^*)]^2[b_{2'}(L^*)]^2+\\ &\quad [b_{1'}(R^*)]^2[b_{3'}(T^*)]^2+[b_{2'}(L^*)]^2[b_{3'}(T^*)]^2,\\ r&=a_3^2-b_3^2=[b_{1'}(R^*)]^2[b_{2'}(L^*)]^2[b_{3'}(T^*)]^2-\\ &\quad [f'(T^*)]^2[g_{1'}(R^*)]^2[g_{2'}(L^*)]^2.\end{aligned}$$

Applying Theorem 1, we have the following results (Ruan and Wei[14]).

Proposition 4 Let ω_0 and τ_0 be defined as in (13) and $h(z)$ be defined as in (9). Suppose that $a_1a_2-a_3-b_3>0$.

(i) If $r\geqslant 0$ and $p^2-3q<0$, then the steady state (R^*,L^*,T^*) of system (18) is absolutely stable (i.e., asymptotically stable for all $\tau\geqslant 0$).

(ii) If $r<0$ or $r\geqslant 0$, $-p+\sqrt{p^2-3q}>0$ and $h\left(\frac{1}{3}(-p+\sqrt{p^2-3q})\right)<0$, then the steady state (R^*,L^*,T^*) of system (18) is asymptotically stable for $\tau\in[0,\tau_0)$.

(iii) If the conditions of (ii) are satisfied, $\tau=\tau_0$, and $h'(\omega_0^2)\neq 0$, then system (18) exhibits a Hopf bifurcation at (R^*,L^*,T^*).

2.3 Delayed models of within-host HIV infection of CD4$^+$ T-cells

HIV targets, among others, the CD4$^+$ T lymphocytes, which are the most abundant white blood cells of the immune system (referred to as helper T cells or CD4$^+$ T-cells). When HIV enters the body, it targets all cells with CD4$^+$ receptors, including the CD4$^+$ T-cells. The gp120 protein on the viral particle binds to the CD4$^+$ receptors on the CD4$^+$ T-cell and injects its core. After an intracellular delay associated with reverse transcription, integration, and the production of capsid proteins, the infected cell releases hundreds of virions that can infect other CD4$^+$ T-cells.

Let $T(t)$, $I(t)$, and $V(t)$ represent the concentration of healthy CD4$^+$ T-cells, the concentration of infected CD4$^+$ T-cells, and the concentration of free HIV at time t, respectively. Consider the following delayed model of within-host HIV infection of CD4$^+$ T-cells (Culshaw and Ruan[15]):

$$\begin{aligned}\frac{dT}{dt}&=s-\mu_TT(t)+rT(t)\left(1-\frac{T(t)+I(t)}{T_{\max}}\right)-k_1T(t)V(t),\\ \frac{dI}{dt}&=k'_1T(t-\tau)V(t-\tau)-\mu_II(t),\\ \frac{dV}{dt}&=N\mu_bI(t)-k_1T(t)V(t)-\mu_VV(t)\end{aligned}\tag{21}$$

under the initial values

$$T(\theta)=T_0,\quad I(0)=0,\quad V(\theta)=V_0,\quad \theta\in[-\tau,0].$$

The parameter s is the source of CD4$^+$ T-cells from precursors, μ_T is the natural death rate of CD4$^+$ T-cells, r is their growth rate (thus, $r>\mu_T$ in general), and $T_{\max}$ is their carrying capacity. k_1 represents the rate of infection of T-cells with free virus and so is given as a loss term for both healthy cells and virus, since they are both lost by binding to one another, and is the source term for infected cells. k'_1 is the rate at which infected cells become actively infected (the ratio k'_1/k_1 is the proportion of T-cells which ever become actively infected). μ_I is a blanket death term for infected cells, to reflect the assumption that we do not initially know whether the cells die naturally or by bursting. In addition, μ_b is the lytic death rate for infected cells. Since N viral particles are released by each lysing cell, this term is multiplied by the parameter N to represent the source for free virus (assuming a one-time initial infection). μ_V is the loss

rate of virus. The positive constant τ represents the length of the intracellular delay in days. System (21) has a (positive) infected steady state $E^*=(T^*,I^*,V^*)$, where

$$T^*=\frac{\mu_V\mu_I}{k'_1N\mu_b-k_1\mu_I},$$
$$I^*=\frac{k'_1T^*V^*}{\mu_I},$$
$$V^*=\frac{\mu_I[(s+(r-\mu_T)T^*)T_{\max}-r(T^*)^2]}{T^*[k'_1rT^*+k_1\mu_IT_{\max}]}.$$

Then the linearized system of (21) at E^* is given by

$$\begin{aligned}\frac{\mathrm{d}X}{\mathrm{d}t}&=-\left(\mu_T+\frac{2rT^*+rI^*}{T_{\max}}+k_1V^*-r\right)X(t)-\\&\quad\frac{rT^*}{T_{\max}}Y(t)-k_1T^*Z(t),\\\frac{\mathrm{d}Y}{\mathrm{d}t}&=k'_1V^*X(t-\tau)-\mu_IY(t)+k_1T^*Z(t-\tau),\quad(22)\\\frac{\mathrm{d}Z}{\mathrm{d}t}&=-k_1V^*X(t)+N\mu_bY(t)-(k_1T^*+\mu_V)Z(t).\end{aligned}$$

The characteristic equation of system (22) is given by

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3+(b_2\lambda+b_3)\mathrm{e}^{-\lambda\tau}=0,\qquad(23)$$

where

$$\begin{aligned}a_1&=\mu_I+\mu_V+k_1T^*+M,\\a_2&=M(k_1T^*+\mu_I+\mu_V)+\mu_I(\mu_V+k_1T^*)-k_1^2T^*V^*,\\a_3&=M\mu_I(\mu_V+k_1T^*)-\mu_Ik_1^2T^*V^*,\\b_2&=k'_1T^*\left(\frac{rV^*}{T_{\max}}-N\mu_b\right),\\b_3&=k'_1T^*\left(k_1N\mu_bV^*+\frac{r\mu_VV^*}{T_{\max}}-MN\mu_b\right).\end{aligned}$$

By Theorem 1, we have the following results (Culshaw and Ruan[15]).

Proposition 5 Suppose that

$$a_1>0,\quad a_3+b_3>0,\quad a_1(a_2+b_2)-(a_3+b_3)>0.$$

Define

$$p=a_1^2-2a_2,\quad q=a_2^2-b_2^2-2a_1a_3,\quad r=a_3^2-b_3^2.$$

(ⅰ) If $r\geqslant0$ and $q>0$, then the infected steady state E^* of model (21) is absolutely stable; that is, asymptotically stable for all $\tau\geqslant0$.

(ⅱ) If either $r<0$ or $r\geqslant0$ and $q<0$, then the infected steady state E^* of model (21) is asymptotically stable when $\tau<\tau_0$ and unstable when $\tau>\tau_0$, where

$$\tau_0=\frac{1}{\omega_0}\arccos\left(\frac{b_2\omega_0^4+(a_1b_3-a_2b_2)\omega_0^2-a_3b_3}{b_3^2+b_2^2\omega_0^2}\right).$$

When $\tau=\tau_0$, a Hopf bifurcation occurs at E^*.

Remark 2 Proposition 5 indicates that the HIV infection model (21) could exhibit Hopf bifurcation at certain value of the delay (and thus periodic oscillations occur in the concentrations of the health and infected $CD4^+$ T-cells) if the parameters satisfy the conditions in (ⅱ). However, there are no clinical data showing that the parameter values satisfy either conditions in (ⅱ). Indeed, there are no data showing that the concentrations of the healthy and infected $CD4^+$ T-cells are periodically oscillatory.

2.4 Delayed models for glucose-insulin system

Diabetes mellitus is a metabolic syndrome characterized by chronic hyperglycemia and relative deficiencies in insulin secretion. Plasma glucose concentration in humans normally lies within a range of 70-100 mg/dL which is vital to life. Blood glucose levels which are too high will result in hyperglycemia. These increased glucose levels are signs of diabetes mellitus and can lead to symptoms such as increased polyuria among others. Conversely, blood glucose levels which are too low can lead to hypoglycemia. Low blood glucose levels below 45-55 mg/100 mL for a period of time can lead to an impairment of brain function, tremors, convulsions, and even death.

One of the intriguing phenomena in human's insulin secretion is ultradian oscillations with period of about 100-200 min. Two basic hypotheses are employed for the description of this phenomenon. The first presumes the existence of an ultradian pancreatic pacemaker producing periodic excitations with periodicity of about 2 hours. The other approach tries to explain ultradian oscillations by specific behavior of a nonlinear system.

To describe the dynamics of the insulin-glucose interaction, let $x(t)$ and $y(t)$ represent the amount (mU) of insulin in plasma and insulin in interstitial fluid at time t, respectively, and glucose space is treated as unique with glucose amount $z(t)$ (mg). Denote by $c_x=x/V_1$(μU/mL), $c_y=y/V_2$(μU/mL), $c_z=0.1z/V_3$ (mg/dL) concentrations of insulin and glucose, in which V_1 is volume of plasma, V_2 is volume of interstitial liquid, and V_3 is volume of the glucose

compartment (L). Drozdov and Khanina[16] proposed the following delayed insulin-glucose model:

$$\begin{aligned}\frac{dx}{dt}&=f_1\left(\frac{0.1z(t)}{V_3}\right)-\left(\frac{E}{V_1}+\frac{1}{T_1}\right)x(t)+\frac{E}{V_2}y(t),\\ \frac{dy}{dt}&=\frac{E}{V_1}x(t)-\left(\frac{E}{V_2}+\frac{1}{T_2}\right)y(t),\\ \frac{dz}{dt}&=f_3\left(\frac{x(t-\tau)}{V_1}\right)-\frac{0.1z(t)}{V_3}f_2\left(\frac{y(t)}{V_2}\right)+(L-p_0),\end{aligned}\tag{24}$$

where

$$f_1(c_z)=\frac{210}{1+\exp(5.21-0.03c_z)}$$

is the insulin secretion rate,

$$f_2(c_y)=\frac{9}{1+\exp\left[7.76-1.772\ln\left(1+V_2/(ET_2)\right)c_y\right]}+0.4$$

is the rate of glucose utilization, and

$$f_3(c_x)=\frac{160}{1+\exp(0.29c_x-7.5)}$$

is the glucose production rate; E, T_1, T_2 (1/min) are parameters, L (mg/min) is the rate of delivery, p_0 is the utilization constant, and τ is a delay in glucose production.

Let $E^*=(x^*,y^*,z^*)$ be the positive equilibrium of system (24). The linearized system of (24) at $E^*=(x^*,y^*,z^*)$ takes the following form:

$$\begin{aligned}\frac{dX}{dt}&=a_{11}X(t)+a_{12}Y(t)+a_{13}Z(t),\\ \frac{dY}{dt}&=a_{21}X(t)+a_{22}Y(t),\\ \frac{dZ}{dt}&=b_{31}X(t-\tau)+a_{32}Y(t)+a_{33}Z(t),\end{aligned}\tag{25}$$

where

$$\begin{aligned}a_{11}&=-\left(\frac{E}{V_1}+\frac{1}{T_1}\right),\quad a_{12}=\frac{E}{V_2},\\ a_{13}&=\frac{0.1}{V_3}\frac{df_1}{dc_z}\left(\frac{0.1z^*}{V_3}\right),\\ a_{21}&=\frac{E}{V_1},\quad a_{22}=-\left(\frac{E}{V_2}+\frac{1}{T_2}\right),\\ b_{31}&=\frac{1}{V_1}\frac{df_3}{dc_x}\left(\frac{x^*}{V_1}\right),\quad a_{32}=-\frac{0.1z^*}{V_2V_3}\frac{df_2}{dc_y}\left(\frac{y^*}{V_2}\right),\\ a_{33}&=-\frac{0.1}{V_3}f_2\left(\frac{y^*}{V_2}\right).\end{aligned}$$

The characteristic equation of the linearized system (25) is

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3+(b_2\lambda+b_3)e^{-\lambda\tau}=0,\tag{26}$$

where

$$\begin{aligned}a_1&=-(a_{11}+a_{22}+a_{33}),\\ a_2&=a_{11}a_{22}+a_{11}a_{33}+a_{22}a_{33}-a_{12}a_{21},\\ a_3&=-a_{11}a_{22}a_{33}-a_{21}a_{12}a_{32},\quad b_2=a_{13}b_{31},\\ b_3&=-a_{22}a_{13}b_{31}.\end{aligned}\tag{26}$$

By Theorem 1, we can similarly establish the stability and bifurcation results for system (24) (see Drozdov and Khanina[16]).

2.5 Delayed models for tumor-immune system interaction

The cell cycle is the process between two cell divisions (or mitosis) and can be divided into 4 phases: resting phase (or gap period) G_1, synthetic period or S phase (where the replication of DNA occurs), post-synthetic phase G_2 (cells complete the DNA replication and enter another gap period), and mitosis M (cells segregate the duplicated sets of chromosomes between daughter cells). There are many facts that prevent the cell from completing the cycle if it detects an abnormality. A cancerous cell does not necessarily divide more rapidly than their normal counterparts, but it loses the ability to regulate the cell cycle, thus proliferation of these cells is not controlled. Once mitosis is completed each daughter cell can enter the cycle again or shift into a quiescent phase G_0, during which cells do not divide for long periods.

To present a competition model of tumor growth that includes the immune system response, Villasana and Radunskaya[17] excluded the quiescent phase, considered three populations: immune system, population of tumor cells during interphase and population of tumor during mitosis, and used a time delay to take into account the phases of the cell cycle. Let $T_I(t)$ denote the population of tumor cells during interphase at time t, where interphase is the pre-mitotic phase, namely G_1+S+G_2. Let $T_M(t)$ be the tumor population during mitosis at time t, $I(t)$ be the immune system population at time t. The governing equations for the system are:

$$\begin{aligned}\frac{dT_I}{dt}&=2a_4T_M(t)-(c_1I(t)+d_2)T_I(t)-a_5T_I(t-\tau),\\ \frac{dT_M}{dt}&=a_5T_I(t-\tau)-d_2T_M(t)-a_4T_M(t)-c_3T_M(t)I(t),\end{aligned}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t}=k+\frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha+(T_I(t)+T_M(t))^n}-c_2T_I(t)I(t)-c_4T_M(t)I(t)-d_1I(t) \quad (27)$$

with continuous initial data

$$T_I(\theta)=\varphi_1(\theta),\quad T_M(\theta)=\varphi_2(\theta),$$
$$I(\theta)=\varphi_3(\theta),\quad \theta\in[-\tau,0].$$

The terms d_2T_I, d_3T_M and d_1I represent proportions of natural cell death or apoptosis, a_4 and a_5 represent the different rates at which cells cycle or reproduce, the c_i terms represent losses from encounters of tumor cells with immune cells and the term $\frac{\rho I(t)(T_I(t)+T_M(t))^n}{\alpha+(T_I(t)+T_M(t))^n}$ describes the nonlinear growth of the immune population due to stimulus by the tumor cells. The parameters ρ,α, and n depend on the type of tumor being considered and the health of the immune system, specifically its ability to produce certain cytokines. In the absence of tumor cells, the immune cells grow at a constant source rate k. The tumor cells reside in interphase for a certain period of time τ before continuing in the cycle to M. Assuming that cells reside in interphase τ units of time, then the cells that enter mitosis at time t are those cells that entered interphase τ units of time before.

Let $E^*=(T_I^*,T_M^*,I^*)$ denote the positive equilibrium of system (27). The characteristic equation of the linearized system of (26) at E^* can be written as

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3+(b_1\lambda^2+b_2\lambda+b_3)\mathrm{e}^{-\lambda\tau}=0. \quad (28)$$

where

$$a_1=P+Q+R,\quad a_2=PQ-c_eT_M^*W+R(P+Q)+Z,$$
$$a_3=PQR-c_3T_M^*(WR-2Za_4)+PZ,$$
$$b_1=a_5,\quad b_2=a_5(P-Q-2a_4),$$
$$b_3=a_5(PQ-c_3T_M^*W-2a_4Q+c_1T_I^*W),$$

in which

$$P=d_3+a_4+c_1I^*,$$
$$Q=c_2T_I^*+c_4T_M^*+d_1-\frac{\rho(T_I^*+T_M^*)^3}{\alpha+(T_I^*+T_M^*)^3},$$
$$R=d_2+c_1I^*,$$
$$W=c_4I^*-\frac{3\alpha I^*(T_I^*+T_M^*)^2}{[\alpha+(T_I^*+T_M^*)^3]^2},$$
$$Z=c_2I^*-\frac{3\alpha I^*(T_I^*+T_M^*)^2}{[\alpha+(T_I^*+T_M^*)^3]^2}.$$

By Theorem 1, once again we can establish the stability and bifurcation results for system (27) (see Villasana and Radunskaya[17]).

3 Discussion

We have studied the distribution of zeros to a general third-order exponential polynomial and provided detailed conditions about when all zeros lie on the left half plane, cross the imaginary axis and enter the right half plane. Since the characteristic equation of the linearized system with delay at a positive equilibrium can be written as a third-order exponential polynomial equation, our results can be used to discuss the local stability and Hopf bifurcation of three-dimensional biological systems with delay. As examples, we applied our results to the three-species delayed food chain models, delayed models for the control of testosterone secretion, delayed models of within-host HIV infection of $CD4^+$ T-cells, glucose-insulin systems with delay, and tumor-immune system interaction models with delay. Many other delayed biological systems (see Batzela and Kappel[18] and Makroglou et al.[19], for example).

If multiple delays appear in the model, techniques in Ruan and Wei[11] can be used to treat multiple delay systems. For example, for the third-order exponential equation with two delays

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3+(b_1\lambda^2+b_2\lambda+b_3)\mathrm{e}^{-\lambda\tau_1}+(c_1\lambda^2+c_2\lambda+c_3)\mathrm{e}^{-\lambda\tau_2}=0,$$

the idea is to consider the case when $\tau_2=0$ first and obtain a critical value $\tau_{1,0}$: all roots have negative real parts when $\tau_1\in[0,\tau_{1,0})$ and at least one root has positive real part when $\tau_1>\tau_{1,0}$. Then fix $\tau_1=\tau_1^*$ in $[0,\tau_{1,0})$, repeat the analysis for τ_2, and find a critical value $\tau_{2,0}(\tau_1^*)$ so that all roots have negative real parts when $\tau_2\in[0,\tau_{2,0}(\tau_1^*))$ and at least one root has positive real part when $\tau_2\geqslant\tau_{2,0}(\tau_1^*)$. Summarizing these results, we know that all roots of the equation with two delays have negative real parts for $(\tau_1,\tau_2)\in[0,\tau_{1,0})\times[0,\tau_{2,0}(\tau_1^*))$. If model parameters depend on the delay, then techniques in Beretta and Kuang[20] can be combined with the methods employed in this paper.

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