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PERIODIC SOLUTIONS FOR SMALL AND LARGE DELAYS IN A TUMOR-IMMUNE SYSTEM MODEL

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Abstract. In this paper we study the Hopf bifurcation for the tumor-immune system model with one delay. This model is governed by a system of two differential equations with one delay. We show that the system may have periodic solutions for small and large delays for some critical value of the delay parameter via Hopf bifurcation theorem bifurcating from the non trivial steady state.

1. Introduction

In this paper, we consider a model that provides a description of tumor cells in competition with the immune system. This description is described by many authors, using ordinary and delayed differential equations to model the competition between immune system and tumor. In particular [26, 31, 32] other similar models can be found in the literature, see, [23, 35, 39] provide a description of the modelling, analysis and control of tumor immune system interaction.

Other authors use kinetic equations to model the competition between immune system and tumor. Although they give a complex description in comparison with other simplest models, they are, for example, needed to model the differences of virulence between viruses, see, [1, 2, 5, 6, 7, 15]. Several other fields of biology use kinetic equations, for instance [19] and [20] give a kinetic approach to describe population dynamics, [2] deals with the development of suitable general mathematical structures including a large variety of Boltzmann type models.

The reader interested in a more complete bibliography about the evolution of a cell, and the pertinent role that have cellular phenomena to direct the body towards the recovery or towards the illness, is addressed to [22, 27]. A detailed description of virus, antivirus, body dynamics can be found in the following references [10, 21, 34, 36]. The mathematical model with which we are dealing, was proposed in a recent paper by M. Galach [26]. In this paper the author developed a new simple model with one delay of tumor immune system competition, this idea is inspired from the paper of Kuznetsov and Taylor (1994) [32] and he recall some numerical

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results of Kuznetsov and Taylor in order to compare them with those obtained in his paper, see, [26].

2. Mathematical model

The mathematical model describing the tumor immune system competition is given by a system of two differential equations with one delay, see Galach [26],

$$\begin{aligned} \frac{dx}{dt} &= \sigma + \omega x(t-\tau)y(t-\tau) - \delta x \\ \frac{dy}{dt} &= \alpha y(1-\beta y) - xy \end{aligned} \tag{2.1}$$

where the parameter ω describes the immune response to the appearance of the tumor cells and the constant τ is the time delay which the immune system needs to develop a suitable response after the recognition of non-self cells. Time delays in connection with the tumor growth also appear in Bodnar and Foryś [12] and [13], Byrne [14], Foryś and Kolev [24] and Foryś and Maciniak-Czochra [25]. For the meaning of the parameters α, β, δ and σ, see Kuznetsov and Taylor [32] and Kirschner and Panetta [31].

For $\tau = 0$ system (2.1) becomes a system of ordinary differential equations:

$$\begin{aligned} \frac{dx}{dt} &= \sigma + \omega xy - \delta x \\ \frac{dy}{dt} &= \alpha y(1-\beta y) - xy \end{aligned} \tag{2.2}$$

In [26], the author study the existence, uniqueness and nonnegativity of solutions and he show the nonexistence of nonnegative periodic solution of system (2.2), using the Dulac-Bendixon criteria, see [37]. The possible nonnegative steady states of system (2.2) and their stability are summarized in the Table 1; see also [26],

Table 1. Nonnegative steady states of system (2.2) and their stability

Region	Conditions	P_0	P_1	P_2
1	$\omega > 0$, $\alpha\delta < \sigma$	stable		
2	$\omega > 0$, $\alpha\delta > \sigma$	unstable		stable
3	$\omega < 0$, $\alpha\delta > \sigma$, $\alpha(\beta\delta-\omega)^2 + 4\beta\omega\sigma > 0$	unstable		stable
4	$\omega < 0$, $\alpha\delta < \sigma$, $\omega + \beta\delta < 0$, $\alpha(\beta\delta-\omega)^2 + 4\beta\omega\sigma > 0$	stable	unstable	stable
5	$\omega < 0$, $\alpha(\beta\delta-\omega)^2 + 4\beta\omega\sigma > 0$	stable		

For $\tau > 0$, the existence and uniqueness of solutions of system (2.1) for every $t > 0$ are established in [26], using the results presented in Hale [29]. Based on the results of Bodnar [11], in [26] the author showed that: (1) If $\omega \geq 0$, these solutions are nonnegative for any nonnegative initial conditions (biologically realistic case). (2) If $\omega < 0$, there exist nonnegative initial condition such that the solution becomes negative in a finite time interval.

Our goal in this paper is to consider the case (1) when $\omega > 0$, which is the most biologically meaningful one. We study the asymptotic behavior of the possible steady states P_0 and P_2 with respect to the delay τ. We establish that, the Hopf bifurcation may occur by using the delay as a parameter of bifurcation. We prove this result for small and large delays.

This paper is organized as follows. In section 3, we recall some results about the absolute and conditional stability of delay equations and the zeros of second order transcendental polynomials. In section 4, we investigate the results presented in section 3 to prove the stability of the possible steady states (trivial and non-trivial) of the delayed system (2.1). The main result of this paper is given in section 5 and section 6. Based on the Hopf bifurcation theorem, we show the occurrence of Hopf bifurcation for small and large delays.

3. Stability of delay equations and zeros of second order transcendental polynomials

In this section we recall some results on the stability of delay equations and on the zero of second order transcendental polynomials.

3.1. Absolute and conditional stability.

Consider the following general nonlinear delay differential system

$$\frac{dx}{dt} = f(x(t), \quad x(t-\tau)), \tag{3.1}$$

where $x \in \mathbb{R}^n$, τ is constant, $f : \mathbb{R}^n \times \mathbb{C}^n \to \mathbb{R}^n$ is smooth enough to guarantee the existence and uniqueness of solutions of (3.1) under the initial condition

$$x(\theta) = \varphi(\theta), \quad \theta \in [-\tau, 0], \tag{3.2}$$

where $C = C([-\tau, 0], \mathbb{R}^n)$. Suppose $f(x^*, x^*) = 0$, that is $x = x^*$ is a steady state of system (3.1).

Definition 3.1. The steady state $x = x^*$ of system (3.1) is called absolutely stable (i.e., asymptotically stable independent of the delay τ) if it is asymptotically stable for all delays $\tau > 0$. $x = x^*$ is called conditionally stable (i.e., asymptotically stable depending of the delay τ) if it is asymptotically stable for τ in some interval, but not necessarily for all delays $\tau > 0$.

The linearized system of (3.1) at $x = x^*$ has the form

$$\frac{dX}{dt} = A_0 X + A_1 X(t-\tau), \tag{3.3}$$

where $X \in \mathbb{R}^n$, A_i $(i = 0, 1)$ is an $n \times n$ constant matrix. Then the characteristic equation associated with system (3.3) takes the form

$$\det[\lambda I - A_0 - A_1 e^{-\lambda\tau}]. \tag{3.4}$$

The location of the roots of some transcendental equation (3.4) in it is general form has been studied by many authors, see Baptistini and Táboas [3], Bellman and Cooke [4], Boese [8], Brauer [9], Cooke and van den Driessche [18], Cooke and Grossman [17], Huang [30], Mahaffy [33], Ruan and Wei [38] an dthe references therein. The following result, which was proved by Chin [16], gives necessary and sufficient conditions for the absolute stability of system (3.3).

Lemma 3.1. *The system* (3.3) *is absolutely stable if and only if*

(i) $\operatorname{Re} \lambda I - A_0 - A_1) < 0$
(ii) $\det[i\zeta - A_0 - A_1 e^{-i\zeta\tau}] \neq 0$ *for all* $\zeta > 0$.

3.2. **A second degree transcendental polynomial.** In this section, we state some results on the second degree transcendental polynomial (see Ruan and Wei [38]). For most system with discrete delay, the characteristic equation of the linearized system at a steady state is a second degree transcendental polynomial equation of the following form:

$$\lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0 \tag{3.5}$$

where p, r, q and s are real numbers. It is known that the steady state is asymptotically stable if all roots of the characteristic equation (3.5) have negative real parts.

Let define the following hypotheses:

(H1) $p + s > 0$.
(H2) $q + r > 0$.
(H3) $(s^2 - p^2 + 2r < 0$ and $r^2 - q^2 > 0)$ or $(s^2 - p^2 + 2r)^2 < 4(r^2 - q^2)$.
(H4) $r^2 - q^2 < 0$ or $(s^2 - p^2 + 2r > 0$ and $(s^2 - p^2 + 2r)^2 = 4(r^2 - q^2))$.
(H5) $r^2 - q^2 > 0$, $s^2 - p^2 + 2r > 0$ and $(s^2 - p^2 + 2r)^2 > 4(r^2 - q^2)$.

Theorem 3.1 ([38]). *Let $\tau_j^{\pm}$ ($j = 0, 1, 2, \dots$) defined by*

$$\tau_j^{\pm} = \frac{1}{\zeta_{\pm}} \arccos\Big\{\frac{q(\zeta_{\pm}^2 - r) - ps\zeta_{\pm}^2}{s^2\zeta_{\pm}^2 + q^2} + \frac{2j\pi}{\zeta_{\pm}}\Big\}, \quad j = 0, 1, 2, \dots$$

where $\zeta_{\pm}$ is given by

$$\zeta_{\pm} = \frac{1}{2}(s^2 - p^2 + 2r) \pm \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{\frac{1}{2}}.$$

(i) If (H1)-(H3) hold, then all roots of equation (3.5) have negative real parts for all $\tau \geq 0$.
(ii) If (H1), (H2) and (H4) hold, then when $\tau \in [0, \tau_0^+)$ all roots of equation (3.5) have negative real parts, when $\tau = \tau_0^+$ equation (3.5) has a pair of purely imaginary roots $\pm i\zeta_{\pm}$, and when $\tau > \tau_0^+$ equation (3.5) has at least one root with positive real part.
(iii) If (H1), (H2) and (H5) hold, then there is a positive integer k such that there are k switches from stability to instability to stability; that is, when $\tau \in [0, \tau_0^+)$, (τ_0^-, τ_0^+), ..., (τ_{k-1}^-, τ_k^+), all roots of equation (3.5) have negative real parts, and when $\tau \in (\tau_0^+, \tau_0^-)$, (τ_1^+, τ_1^-), ..., $(\tau_{k-1}^+, \tau_{k-1}^-)$, and $\tau > \tau_k^+$, equation (3.5) has at least one root with positive real part.

Remark 3.1. Theorem 3.1 was obtained by Cooke and Grossman [17] in analyzing a general second order equation with delayed friction and delayed restoring force. for other related work, see, Baptistini and Táboas [3], Bellman and Cooke [4], Boese [8], Brauer [9], Cooke and van den Driessche [18], Cooke and Grossman [17], Huang [30], Mahaffy [33], Ruan and Wei [38], etc.

4. Steady states and stability for positive delays

Consider the system (2.1), and suppose that $\omega > 0$. From the table 1 (see, section 2), we distingue between two cases: $\alpha\delta < \sigma$ and $\alpha\delta > \sigma$.

Case 1: $\omega > 0$ and $\alpha\delta < \sigma$. The system (2.1) has a unique positive equilibrium P_0 given by $P_0 = (\frac{\sigma}{\delta}, 0)$ and the linearized system around P_0 takes the form

$$\begin{aligned} \frac{dx}{dt} &= \omega\frac{\sigma}{\delta}y(t-\tau) - \delta x \\ \frac{dy}{dt} &= (\alpha - \frac{\sigma}{\delta})y \end{aligned} \tag{4.1}$$

which leads to the characteristic equation

$$W(\lambda) = (\lambda + \frac{\sigma}{\delta} - \alpha)(\lambda + \delta). \tag{4.2}$$

Then we have the following result.

Proposition 4.1. *Under the hypotheses $\omega > 0$ and $\alpha\delta < \sigma$, the equilibrium point P_0 is absolutely stable.*

Proof. From the characteristic equation (4.2) and lemma 3.1, it is easy to obtain the result (see, [28, 29]). □

Case 2: $\omega > 0$ and $\alpha\delta > \sigma$. In this case, system (2.1) has two equilibrium points (see, Table 1) $P_0 = (\frac{\sigma}{\delta}, 0)$ and $P_2 = (x_2, y_2)$ where

$$x_2 = \frac{-\alpha(\beta\delta - \omega) + \sqrt{\Delta}}{2\omega}, \quad y_2 = \frac{\alpha(\beta\delta + \omega) - \sqrt{\Delta}}{2\alpha\beta\omega}$$

with $\Delta = \alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega$. From the characteristic equation (4.2), we deduce the following result.

Proposition 4.2. *Under the hypotheses $\omega > 0$ and $\alpha\delta > \sigma$, the equilibrium point P_0 is unstable for all positive time delay.*

Proof. For the proof of this proposition, from the characteristic equation (4.2). It is obvious to check the result. □

In the next, we shall study the stability of the non-trivial equilibrium point P_2. Let $u = x - x_2$ and $v = y - y_2$, by linearizing system (2.1) around the non-trivial equilibrium point P_2, we obtain the linear system

$$\begin{aligned} \frac{du}{dt} &= \omega x_2 v(t-\tau) - \omega y_2 u(t-\tau) - \delta u \\ \frac{dv}{dt} &= -y_2 u + (\alpha - 2\alpha\beta y_2 - x_2)v \end{aligned} \tag{4.3}$$

The characteristic equation of equation (4.3) has the form

$$W(\lambda, \tau) = \lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \tag{4.4}$$

which is the same equation presented in section 3.2. Where $p = \delta + \alpha\beta y_2 > 0$, $r = \delta\alpha\beta y_2 > 0$, $s = -\omega y_2 < 0$ and $q = \alpha\omega y_2(1 - 2\beta y_2) > 0$. The stability of the equilibrium point P_2 is a result of the localization of the roots of the equation

$$W(\lambda, \tau) = 0.$$

Then we have the following theorem.

Theorem 4.1. *Assume $0 < \frac{\omega}{\beta} < \alpha$, $\alpha\delta > \sigma$, $\alpha > 0$ and $\beta > 0$. Then P_2 is conditionally stable.*

Proof. From the expressions of p, q, s and r and the paper [26], we have $p + s > 0$ and $q + r > 0$. Therefore, the hypotheses (H1), (H2) are satisfied and the steady state P_2 is asymptotically stable (see section 3.2) for $\tau = 0$. Since $r^2 - q^2 = \alpha^2 y_2^2(\delta^2\beta^2 - \omega^2(1 - 2\beta y_2)^2)$, the sign of $r^2 - q^2$ is deduced from the sign of $(\delta\beta - \omega^2(1 - 2\beta y_2)) = -2\alpha\omega - \sqrt{\Delta}$ which is negative.
Therefore, $r^2 - q^2 < 0$

Now, we compute $s^2 - p^2 + 2r$. From the expressions of p, s and r, we have

$$s^2 - p^2 + 2r = (\omega - \alpha\beta)(\omega + \alpha\beta)y^2 - \delta^2.$$

As $\frac{\omega}{\beta} < \alpha$, we have

$$s^2 - p^2 + 2r < 0$$

and the hypothesis (H4) of section 3.2 is satisfied. From theorem 3.1 (ii), the equilibrium point P_2 is conditionally stable and there exist τ_l such that: P_2 is asymptotically stable for $\tau \in [0, \tau_l)$ and unstable for $\tau > \tau_l$. For $\tau = \tau_l$ the characteristic equation (4.4) has a pair of purely imaginary roots $\pm i\zeta$, where

$$\tau_l = \frac{1}{\zeta_l} \arccos\Big\{\frac{q(\zeta_l^2 - r) - ps\zeta_l^2}{s^2\zeta_l^2 + q^2}\Big\}, \tag{4.5}$$

$$\zeta_l = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{1/2}. \tag{4.6}$$

□

In the next sections, we will study the occurrence of Hopf bifurcation for smaller and larger delays.

Notation: The index s is designed for small time delays and the index l is designed for large time delays.

Let $z(t) = (u(t), v(t)) = (x(t), y(t)) - (x_2, y_2)$, then the system (2.1) is written as a functional differential equation (FDE) in $C := C([-\tau, 0], \mathbb{R}^2)$:

$$\frac{dz(t)}{dt} = L(\tau)z_t + f(z_t, \tau) \tag{4.7}$$

where $L(\tau) : C \to \mathbb{R}^2$ is a linear operator and $f : C \times \mathbb{R} \to \mathbb{R}^2$ are given respectively by

$$L(\tau)\varphi = \begin{pmatrix} \omega y_2\varphi_1(-\tau) + \omega x_2\varphi_2(-\tau) - \delta\varphi_1(0) \\ -y_2\varphi_1(0) + (\alpha - 2\alpha\beta y_2 - x_2)\varphi_2(0) \end{pmatrix}$$

and

$$f(\varphi, \tau) = \begin{pmatrix} \sigma + \omega\varphi_1(-\tau)\varphi_2(-\tau) + \omega x_2 y_2 - \delta x_2 \\ -\alpha\beta\varphi_2^2(0) + \alpha y_2 - \alpha\beta y_2^2 - \varphi_1(0)\varphi_2(0) - x_2 y_2 \end{pmatrix}$$

for $\varphi = (\varphi_1, \varphi_2) \in C$.

5. Hopf bifurcation occurrence for small delays

For small delays, let $e^{-\lambda\tau} \simeq 1 - \lambda\tau$, then the characteristic equation (4.4) becomes

$$W_0(\lambda, \tau) = (1 - s\tau)\lambda^2 + (p + s - q\tau)\lambda + r + q = 0. \tag{5.1}$$

Since the equilibrium point P_2 is asymptotically stable for $\tau = 0$, by Rouche's theorem, there exist τ_s such that P_2 asymptotically stable for $\tau < \tau_s$ and unstable for $\tau > \tau_s$, where τ_s is the value for which the characteristic equation (5.1) has a pair of purely imaginary roots. Let $\lambda = i\zeta$, then $W_0(i\zeta, \tau) = 0$ if and only if

$$\begin{gathered} (1 - s\tau)\zeta^2 - q - r = 0, \\ p + s - q\tau = 0\,. \end{gathered} \tag{5.2}$$

Then, from the second equation of (5.2), we have $\tau_s = \frac{p+s}{q}$ and $\zeta_s = \sqrt{\frac{q(q+r)}{q-s(p+s)}}$.

We deduce the following result of stability of the non-trivial equilibrium point P_2 for small delays.

Theorem 5.1. *Assume $0 < \omega/\beta < \alpha$, $\alpha\delta > \sigma$, $\alpha > 0$ and $\beta > 0$. Then, there exists τ_s such that: P_2 is asymptotically stable for $\tau \in [0, \tau_s)$ and unstable for $\tau > \tau_s$. For $\tau = \tau_s$ the characteristic equation (5.1) has a pair of purely imaginary roots $\pm i\zeta_s$, where $\tau_s = \frac{p+s}{q}$ and $\zeta_s = \sqrt{\frac{q(q+r)}{q-s(p+s)}}$.*

Proof. Since $q - s(p+s) = q + \omega\delta y_2 + \omega y_2^2(\alpha\beta - \omega)$ and $q > 0$ and from the hypothesis $\alpha\beta > \omega$, we have $p + s > 0$ and $q - s(p + s) > 0$. Then the quantities of $\tau_s = \frac{p+s}{q}$ and $\zeta_s = \sqrt{\frac{q(q+r)}{q-s(p+s)}}$ are well defined. □

Now, we apply the Hopf bifurcation theorem, see [28], to show the existence of a non-trivial periodic solutions of system (4.7) bifurcating from the non trivial steady state P_2. We use the delay as a parameter of bifurcation. Therefore, the periodicity is a result of changing the type of stability, from stationary solution to limit cycle.

Next we state the main result of this paper for small delays.

Theorem 5.2. *Assume $0 < \omega/\beta < \alpha$, $\alpha\delta > \sigma$, $\alpha > 0$ and $\beta > 0$. There exists $\varepsilon_s > 0$ such that, for each $0 \le \varepsilon < \varepsilon_s$, equation (4.7) has a family of periodic solutions $p_s(\varepsilon)$ with period $T_s = T_s(\varepsilon)$, for the parameter values $\tau = \tau(\varepsilon)$ such that $p_s(0) = P_2$, $T_s(0) = \frac{2\pi}{\zeta_s}$ and $\tau(0) = \tau_s$, where $\tau_s = \frac{p+s}{q}$ and $\zeta_s = \sqrt{\frac{q(q+r)}{q-s(p+s)}}$ are given in equation (5.2).*

Proof. We apply the Hopf bifurcation theorem introduced in [28]. From the expression of f in (4.7), we have

$$f(0, \tau) = 0 \quad \text{and} \quad \frac{\partial f(0, \tau)}{\partial \varphi} = 0, \quad \text{for all } \tau > 0$$

From equation (5.2) and theorem 5.1, the characteristic equation (5.1) has a pair of simple imaginary roots $\lambda_s = i\zeta_s$ and $\overline{\lambda}_s = -i\zeta_s$ at $\tau = \tau_s$.

Next, we need to verify the transversality condition. From equation (5.1), $W_0(\lambda_s, \tau_s) = 0$ and $\frac{\partial}{\partial\lambda} W_0(\lambda_s, \tau_s) = 2\lambda_s(1 - s\tau_s) \neq 0$. According to the implicit function theorem, there exists a complex function $\lambda = \lambda(\tau)$ defined in a neighborhood of τ_s, such that $\lambda(\tau_s) = \lambda_s$ and $W_0(\lambda(\tau), \tau) = 0$ and

$$\lambda'(\tau) = -\frac{\partial W_0(\lambda, \tau)/\partial\tau}{\partial W_0(\lambda, \tau)/\partial\lambda}, \tag{5.3}$$

for τ in a neighborhood of τ_s. Letting, $\lambda(\tau) = p(\tau) + iq(\tau)$, from (5.3) we have

$$p'(\tau)_{/\tau=\tau_s} = \frac{q}{2(1 - s\tau_s)}\,.$$

From the hypothesis $0 < \omega/\beta < \alpha$, we conclude that

$$p'(\tau)_{/\tau=\tau_s} > 0,$$

which completes the proof. □

6. Hopf bifurcation occurrence for large delays

For large delays τ, let $\lambda = \kappa + i\zeta$. According to the Hopf bifurcation theorem [28], we come to the main result of this paper for large time delays.

Theorem 6.1. *Assume* $0 < \omega/\beta < \alpha$, $\alpha\delta > \sigma$, $\alpha > 0$, $\beta > 0$ *and* δ *close to* 0*. There exists* $\varepsilon_1 > 0$ *such that, for each* $0 \le \varepsilon < \varepsilon_1$*, equation* (4.7) *has a family of periodic solutions* $p_l(\varepsilon)$ *with period* $T_l = T_l(\varepsilon)$*, for the parameter values* $\tau = \tau(\varepsilon)$ *such that* $p_l(0) = P_2$*,* $T_l(0) = \frac{2\pi}{\zeta_l}$ *and* $\tau(0) = \tau_l$*, where* τ_l *and* ζ_l *are given respectively in equations* (4.5) *and* (4.6)*.*

Proof. As in the previous section, we apply the Hopf bifurcation theorem introduced in [28]. From the expression of f in (4.7), we have,

$$f(0,\tau) = 0 \quad \text{and} \quad \frac{\partial f(0,\tau)}{\partial \varphi} = 0, \quad \text{for all } \tau > 0$$

From equation (4.4) and theorem 4.1, the characteristic equation (4.4) has a pair of simple imaginary roots $\lambda_l = i\zeta_l$ and $\overline{\lambda}_l = -i\zeta_l$ at $\tau = \tau_l$. From equation (4.4), $W(\lambda_l, \tau_l) = 0$ and $\frac{\partial}{\partial\lambda} W(\lambda_l, \tau_l) = 2i\zeta_l + p + (s - \tau(is\zeta_l + q))e^{-i\zeta_l\tau_l} \neq 0$. According to the implicit function theorem, there exists a complex function $\lambda = \lambda(\tau)$ defined in a neighborhood of τ_l, such that $\lambda(\tau_l) = \lambda_l$ and $W(\lambda(\tau), \tau) = 0$ and

$$\lambda'(\tau) = -\frac{\partial W(\lambda,\tau)/\partial\tau}{\partial W(\lambda,\tau)/\partial\lambda}, \tag{6.1}$$

for τ in a neighborhood of τ_l. Then

$$\lambda'(\tau) = -\lambda \frac{s\lambda^3 + (s^2 p + q)\lambda^2 + (sr + pq)\lambda + qr}{\tau s\lambda^3 + (s + \tau(sp + q))\lambda^2 + (2q + \tau(sr + pq))\lambda + pq - sr + qr} \tag{6.2}$$

From equation (6.2) we have

$$\kappa'(\tau)\big|_{\tau=\tau_l} = \zeta_l^2 \frac{s^2\zeta_l^4 + (sqr(\tau - 1) + 2q^2)\zeta_l^2 + sr^2(q - sr) + pq^2(p + r) - qr(2q + \tau(sr + pq))}{A^2 + B^2}, \tag{6.3}$$

where

$$A = -(s + \tau(sp + q))\zeta_l^2 + pq - sr + qr,$$
$$B = -\tau s\zeta_l^2 + (2q + \tau(sr + pq))\zeta_l.$$

From the expression of r, when δ is close to 0, then r is very small. From equation (6.3), we conclude that,

$$\kappa'(\tau)_{/\tau=\tau_l} > 0$$

Therefore, the transversality condition is verified, which completes the proof. □

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