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Change in criticality of Hopf bifurcation in a time-delayed cancer model

Israel Ncube and **Kiara M. Martin**

Alabama A & M University, Department of Mathematics,
4900 Meridian Street North, Huntsville, AL 35762, U.S.A.

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Abstract. The main goal of this work is to conduct a rigorous study of a mathematical model that was first proposed by Gałach (2003). The model itself is an adaptation of an earlier model proposed by Kuznetsov et al. (1994), and attempts to describe the interaction that exists between immunogenic tumour cells and the immune system. The particular adaptation due to Gałach (2003) consists of replacing the Michaelis–Menten function of Kuznetsov et al. (1994) by a Lotka–Volterra form instead, and incorporating a single discrete time delay in the latter to account for the biophysical fact that the immune system takes finite, non-zero time to mount a response to the presence of immunogenic tumour cells in the body. In this work, we perform a linear stability analysis of the model's three equilibria, and formulate a local Hopf bifurcation theorem for one of the two endemic equilibria. Furthermore, using centre manifold reduction and normal form theory, we characterise the criticality of the Hopf bifurcation. Our theoretical results are supported by some sample numerical plots of the Poincaré–Lyapunov constant in an appropriate parameter space. In a sense, our work in this article complements and significantly extends the work initiated by Gałach (2003).

Keywords: delay differential equations, cancer, tumour, equilibria, Hopf bifurcation, criticality.

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1 Introduction

It is well-known [1, 2, 10–15, 17, 18] that when immunogenic tumours and other foreign entities appear in the body, the body's immune system mounts an appropriate response aimed at eliminating them. The immune response to the appearance of an immunogenic tumour is typically cell-mediated [1]. Cytotoxic T lymphocytes (CTL) and natural killer cells (NK) are known to play a leading role in the immune response [1, 17, 18]. The interaction between the immune system and tumour cells in vivo is presently poorly understood. Nonetheless, a great number of mathematical models whose goal it is to emulate this interaction between the immune system and immunogenic tumour cells have been developed over the years (see

✉ Corresponding author. Email: Ncube.Israel@gmail.com

[1, 10–15, 17, 18] and references contained therein). In our view, the impact of the seminal work of Kuznetsov et al. [1] partially lies in the fact that they were able to estimate some biophysically important model parameters that could otherwise not be measured in vivo. Consequently, their model shows a comparatively high degree of fidelity with existing experimental data. The model studied by [1] is premised on the idea of cell-mediated immune response to a growing tumour cell population [1], and incorporates infiltration of tumour cells by cytotoxic effector cells (e.g. CTL or NK cells) and the possibility of effector cell inactivation [1]. Much of the analysis in [1] relies on mathematical machinery from numerical bifurcation theory in classical dynamics, and the primary goal is to elucidate the why and the wherefore of *tumour dormancy* and the paradoxical phenomenon of *sneaking through* [1,17,18]. It is important to point out at the onset that Kuznetsov et al. [1] assume in their study that the immune response elicited by the presence of immunogenic tumour cells is instantaneous, which, of course, is contrary to biophysical reality. There is a vast body of mathematical models in the literature (see [10–15] and references contained therein) that do make the same assumption of instantaneous immune response, which, of course, is the metaphorical Achilles' heel of all such models. Ghosh and collaborators [12–15] study developments and refinements of the cancer model posited by [1]. They employ ideas from optimal control theory to devise strategies for eliminating the cancer [15] in the non-delayed model of [1]. In [14], the authors investigate the effects of anti-cancer drugs used in tandem with chemotherapy on the dynamics of a non-delayed mathematical model of cancer. Ghosh et al. [13] considered the question of whether tumour growth is impacted by time delayed interactions between cancerous cells and the microenvironment in which they are embedded. They incorporated two discrete time delays in the cancer model studied, one describing the time-delayed interactions that occur between tumour cells and immune cells [13], whilst the other one describes the time-delayed immune response to the presence of tumour or non-self cells. It is important to note that the stability of equilibria in models with two discrete time delays has been extensively, and exhaustively, studied in the literature [23–26]. For instance, it is now well-known that the presence of two time delays can destabilise equilibria, induce stability switching, and lead to the emergence of codimension two bifurcation points [23, 26]. Khajanchi et al. [12] looked at the effects of discrete time delay in a chaotic mathematical model of cancer, and studied the ensuing Hopf bifurcation problem with the time delay used as the bifurcation parameter.

The Kuznetsov et al. [1] mathematical model is described by the following system of two coupled nonlinear ordinary differential equations.

$$\begin{cases} \frac{dx}{d\tau} = \sigma + F(x,y) - \mu xy - \overline{\delta} x \,, \\ \frac{dy}{d\tau} = \alpha y(1-\beta y) - xy \,, \end{cases} \tag{1.1}$$

where x and y denote the rescaled dimensionless densities of effector cells (ECs) and tumour cells (TCs), respectively; and τ in this case denotes rescaled time. The function $F(x,y)$ is given by $F(x,y) := \rho xy/(\eta + y)$, a Michaelis–Menten type function, and describes the rate at which cytotoxic ECs congregate in the neighbourhood of an immunogenic TC [1]. The seven dimensionless parameters σ, ρ, η, μ, $\overline{\delta}$, α, and β appearing in (1.1) are described and estimated in [1] as adumbrated in Table 1.1.

The model due to Gałach [2] is an adaptation of (1.1), and is given by

$$\begin{cases} x'(t) = \sigma + Wx(t-\tau)y(t-\tau) - \overline{\delta} x \,, \\ y'(t) = \alpha y(1-\beta y) - xy \,, \end{cases} \tag{1.2}$$

Parameter	Estimated value
σ	0.1181
ρ	1.131
η	20.19
μ	0.00311
$\bar{\delta}$	0.3743
α	1.636
β	2.0×10^{-3}

Table 1.1: Estimates of the Kuznetsov et al. [1] model parameter values.

where $\tau > 0$ is a discrete time delay representing the time it takes for the immune system to respond to the presence of TCs, t is rescaled time (what is denoted by τ in (1.1)), and the parameter $W \in \mathbb{R}$ describes the aggregation of ECs in the neighbourhood of an immunogenic TC [2]. In fact, Gałach [2] defines the parameter W as

$$W := \frac{\theta - m}{n}, \quad \text{where } \theta, m \in \mathbb{R}^+,\ n = 1.101 \times 10^{-7}. \tag{1.3}$$

The definition of W given in (1.3) implies that $\operatorname{sgn}(W) = \operatorname{sgn}(\theta - m)$. It is also assumed that $x(\theta) = x_0$ and $y(\theta) = y_0$ for $\theta \in [-\tau, 0]$, where x_0 and y_0 are non-negative continuous initial functions. It is important to note that Gałach [2] assumed the function $F(x,y)$ of the form $F(x,y) := Wxy$, instead of the Michaelis–Menten function adopted by Kuznetsov et al. [1]. In addition, Gałach [2] introduced a single discrete time delay $\tau > 0$ in the function $F(x,y)$, to capture the fact that it takes non-zero time for ECs to congregate in the neighbourhood of an immunogenic TC. The remaining parameters $\sigma, \bar{\delta}, \alpha$, and β are positive and are as defined in [1].

Let $(\bar{x}, \bar{y})$ denote a generic equilibrium of (1.2). The equilibria of (1.2) are obtained by solving the system of algebraic equations

$$\begin{cases} 0 = \sigma + W\bar{x} \cdot \bar{y} - \bar{\delta}\bar{x}\,, \\ 0 = \alpha\bar{y}(1 - \beta\bar{y}) - \bar{x} \cdot \bar{y}\,. \end{cases} \tag{1.4}$$

The cancer-free equilibrium $\left(\sigma/\bar{\delta}, 0\right)$ always exists [2]. If $\phi := \alpha^2(\beta\bar{\delta} - W)^2 + 4\alpha\beta W\sigma > 0$, then, additionally, two endemic (chronic) equilibria exist [2], namely: $(\bar{x}_+, \bar{y}_+)$ and $(\bar{x}_-, \bar{y}_-)$, where

$$\begin{cases} \bar{x}_+ := \frac{-\alpha(\beta\bar{\delta} - W) - \sqrt{\phi}}{2W}\,, \\ \bar{y}_+ := \frac{\alpha(\beta\bar{\delta} + W) + \sqrt{\phi}}{2\alpha\beta W}\,, \end{cases} \tag{1.5}$$

and

$$\begin{cases} \bar{x}_- := \frac{-\alpha(\beta\bar{\delta} - W) + \sqrt{\phi}}{2W}\,, \\ \bar{y}_- := \frac{\alpha(\beta\bar{\delta} + W) - \sqrt{\phi}}{2\alpha\beta W}\,. \end{cases} \tag{1.6}$$

The current paper will accomplish the following.

1. Give a complete characterisation of the linear stability of the three equilibria of (1.2). It is worth noting that Gałach [2] attempted to study the linear stability of the cancer-free equilibrium of (1.2), but the corresponding characteristic equation derived in the ensuing analysis is erroneous, and so the results obtained are compromised (see [2, Lemma 9, page 401]).

2. Give a complete account of the local Hopf bifurcation of the endemic equilibria, including characterisation of its criticality via centre manifold reduction and normal form theory. This aspect of the problem was not visited by Gałach [2], save for the comment that "*. . . the analysis of stability for the remaining steady states is much more complicated. . .*" in [2, page 402]. Furthermore, Gałach [2] did note that oscillations appear in the solutions to (1.2), a phenomenon that is non-existent as far as solutions of (1.1) are concerned. In fact, Gałach [2] was able to perform some numerical simulations of solutions of (1.2) and (1.1), with some parameters fixed, and was able to exhibit oscillatory solutions of the former, in particular. However, no mention of Hopf bifurcation is made, and there is no discussion about the stability of bifurcated oscillatory solutions.

Thus, in a nutshell, the primary objective of the present work is to correct, extend, and complement the analysis of the system (1.2) initiated by Gałach [2].

2 Linear stability of equilibria

This section focusses on the complete characterisation of the linear stability of the three equilibria of (1.2).

2.1 The cancer-free equilibrium $(\sigma/\overline{\delta}, 0)$

We begin our study by analysing the linear stability of the cancer-free equilibrium, $(\sigma/\delta, 0)$. To facilitate the analysis to come, we perform the following change-of-variables. Let $\widetilde{y}(t) = y(t) - 0$ and $\widetilde{x}(t) = x(t) - \sigma/\overline{\delta}$. Thus, the system (1.2) transforms to

$$\begin{cases} \widetilde{x}'(t) = W\widetilde{x}(t-\tau)\cdot\widetilde{y}(t-\tau) + \frac{W\sigma}{\overline{\delta}}\widetilde{y}(t-\tau) - \overline{\delta}\widetilde{x}(t) := H_1 \,, \\ \widetilde{y}'(t) = \left(\alpha - \frac{\sigma}{\overline{\delta}}\right)\widetilde{y}(t) - \alpha\beta\widetilde{y}^2(t) - \widetilde{x}(t)\cdot\widetilde{y}(t) := H_2 \,. \end{cases} \tag{2.1}$$

It is important to note that the trivial equilibrium $(0, 0)$ of the transformed system (2.1) is equivalent to the cancer-free equilibrium of (1.2). This observation has critical implications on the analysis to come. For mathematical convenience, we adopt the following notation from [3]: $\widetilde{x}|_\tau := \widetilde{x}(t-\tau)$ and $\widetilde{y}|_\tau := \widetilde{y}(t-\tau)$. We obtain from (2.1) the matrices

$$\left.\begin{pmatrix} \frac{\partial H_1}{\partial \widetilde{x}|_\tau} & \frac{\partial H_1}{\partial \widetilde{y}|_\tau} \\ \frac{\partial H_2}{\partial \widetilde{x}|_\tau} & \frac{\partial H_2}{\partial \widetilde{y}|_\tau} \end{pmatrix}\right|_{(0,0)} = \left.\begin{pmatrix} \omega\widetilde{y}(t-\tau) & \omega\widetilde{x}(t-\tau) + \frac{\omega\sigma}{\overline{\delta}} \\ 0 & 0 \end{pmatrix}\right|_{(0,0)} = \begin{pmatrix} 0 & \frac{W\sigma}{\overline{\delta}} \\ 0 & 0 \end{pmatrix}, \tag{2.2}$$

and

$$\left.\begin{pmatrix} \frac{\partial H_1}{\partial \widetilde{x}} & \frac{\partial H_1}{\partial \widetilde{y}} \\ \frac{\partial H_2}{\partial \widetilde{x}} & \frac{\partial H_2}{\partial \widetilde{y}} \end{pmatrix}\right|_{(0,0)} = \left.\begin{pmatrix} -\overline{\delta} & 0 \\ -\widetilde{y} & \alpha - \frac{\sigma}{\overline{\delta}} - 2\alpha\beta\widetilde{y} - \widetilde{x} \end{pmatrix}\right|_{(0,0)} = \begin{pmatrix} -\overline{\delta} & 0 \\ 0 & \alpha - \frac{\sigma}{\overline{\delta}} \end{pmatrix}. \tag{2.3}$$

From (2.2) and (2.3), we have that the linearisation of (2.1) about $(0, 0)$ is

$$\begin{cases} \widetilde{x}'(t) = -\delta\widetilde{x}(t) + \frac{W\sigma}{\overline{\delta}}\widetilde{y}(t-\tau) \,, \\ \widetilde{y}'(t) = \left(\alpha - \frac{\sigma}{\overline{\delta}}\right)\widetilde{y}(t) \,. \end{cases} \tag{2.4}$$

We now assume the ansatz $\widetilde{x}(t) = c_1 e^{\lambda t}$, $\widetilde{y}(t) = c_2 e^{\lambda t}$, where $c_1, c_2 \in \mathbb{R}$ and $\lambda \in \mathbb{C}$. Substituting this into (2.4) yields the matrix equation

$$\begin{pmatrix} \lambda + \overline{\delta} & -\frac{W\sigma}{\overline{\delta}}e^{-\lambda\tau} \\ 0 & \lambda - \alpha + \frac{\sigma}{\overline{\delta}} \end{pmatrix}\begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \tag{2.5}$$

which admits non-trivial solutions $c_1, c_2 \neq 0$ if, and only if,

$$\det \begin{pmatrix} \lambda + \overline{\delta} & -\frac{\omega\sigma}{\overline{\delta}} e^{-\lambda\tau} \\ 0 & \lambda - \alpha + \frac{\sigma}{\overline{\delta}} \end{pmatrix} = 0 \,. \tag{2.6}$$

Equation (2.6) leads to the characteristic equation

$$(\lambda + \overline{\delta}) \left(\lambda - \alpha + \frac{\sigma}{\overline{\delta}} \right) = 0 \,, \tag{2.7}$$

which differs from the one erroneously obtained in [2], where a characteristic quasi-polynomial was obtained instead. As has been shown here, the characteristic equation corresponding to the cancer-free equilibrium is a quadratic polynomial, which is quite straightforward to analyse. We arrive at our first delay-independent stability result.

Theorem 2.1. *A necessary and sufficient condition for the local asymptotic stability of the cancer-free equilibrium is that $\sigma/\overline{\delta} > \alpha$. That is, the density of effector cells must surpass the threshold α.*

Proof. The roots of the characteristic equation (2.7) are $\lambda_1 = -\overline{\delta} < 0$ and $\lambda_2 = \alpha - (\sigma/\overline{\delta})$. It is clear that $\lambda_2 < 0$ if, and only if, $\sigma/\overline{\delta} > \alpha$. The result follows. □

Our Theorem 2.1 contradicts the results of [2, Lemma 9]. The stability of the cancer-free equilibrium is independent of the immune response time delay, as we have established here.

2.2 The endemic equilibria $(\overline{x}_+, \overline{y}_+)$ and $(\overline{x}_-, \overline{y}_-)$

Endemic equilibria represent a state of affairs in which the body always has a certain fixed non-zero density of both effector cells and tumour cells. They are essentially chronic disease steady states. Our analysis here will focus entirely on the endemic equilibrium $(\overline{x}_+, \overline{y}_+)$. Analysis of the equilibrium $(\overline{x}_-, \overline{y}_-)$ is identical to that of $(\overline{x}_+, \overline{y}_+)$. To begin, let $\widetilde{x}(t) = x(t) - \overline{x}_+$ and $\widetilde{y}(t) = y(t) - \overline{y}_+$. Thus, the nonlinear system (1.2) is transformed to the equivalent system

$$\begin{cases} \widetilde{x}'(t) = \left(\sigma + W\overline{x}_+ \cdot \overline{y}_+ - \overline{\delta}\overline{x}_+\right) + W\overline{y}_+\widetilde{x}(t-\tau) + W\overline{x}_+\widetilde{y}(t-\tau) - \overline{\delta}\widetilde{x}(t) + W\widetilde{x}(t-\tau)\widetilde{y}(t-\tau) \\ \qquad =: G_1, \\ \widetilde{y}'(t) = \left[\alpha\left(1 - 2\beta\overline{y}_+\right) - \overline{x}_+\right]\widetilde{y}(t) - \overline{y}_+\widetilde{x}(t) - \alpha\beta\widetilde{y}^2(t) - \widetilde{x}(t)\widetilde{y}(t) - \alpha\beta\overline{y}_+^2(t) + (\alpha - \overline{x}_+)\,\overline{y}_+ \\ \qquad =: G_2. \end{cases} \tag{2.8}$$

Consequently, the linearisation of (2.8) about the equilibrium $(0,0)$ is given by

$$\begin{cases} \widetilde{x}'(t) = -\overline{\delta}\widetilde{x}(t) + W\overline{y}_+\widetilde{x}(t-\tau) + \omega\overline{x}_+\widetilde{y}(t-\tau) \,, \\ \widetilde{y}'(t) = -\overline{y}_+\widetilde{x}(t) + \left[\alpha\left(1 - 2\beta\overline{y}_+\right) - \overline{x}_+\right]\widetilde{y}(t) \,. \end{cases} \tag{2.9}$$

The corresponding characteristic equation is the quasi-polynomial

$$\Delta(\lambda) := \lambda^2 + \left(\psi_1 + \overline{\delta}\right)\lambda + \overline{\delta}\psi_1 + \left(\psi_3 - \lambda\psi_2 - \psi_1\psi_2\right)e^{-\lambda\tau} = 0 \,, \tag{2.10}$$

where

$$\begin{cases} \psi_1 := -\alpha + 2\alpha\beta\overline{y}_+ + \overline{x}_+ \,, \\ \psi_2 := W\left(1 + \overline{y}_+\right) \,, \\ \psi_3 := W\overline{y}_+\overline{x}_+ \,. \end{cases} \tag{2.11}$$

Lemma 2.2. *If* $\overline{\delta}\psi_1 + \psi_3 - \psi_1\psi_2 = 0$, *then* $\lambda = 0$ *is always a root of* (2.10), $\forall\tau \geq 0$.

Proof. The result follows by noting from (2.10) that $\Delta(0) = \overline{\delta}\psi_1 + \psi_3 - \psi_1\psi_2$. □

Theorem 2.3. *If* $\overline{\delta}\psi_1 + \psi_3 - \psi_1\psi_2 < 0$, *then the endemic equilibrium* $(\overline{x}_+, \overline{y}_+)$ *is unstable.*

Proof. We note from (2.10) that $\Delta(0) = \overline{\delta}\psi_1 + \psi_3 - \psi_1\psi_2 < 0$, by hypothesis. The continuity of $\Delta(\lambda)$ and the Intermediate Value Theorem yield $\lim_{\lambda\to+\infty}\Delta(\lambda) = +\infty$. Thus, the characteristic equation (2.10) has at least one positive real root, and the endemic equilibrium $(\overline{x}_+, \overline{y}_+)$ is unstable. This completes the proof. □

If $\tau = 0$, then (2.10) reduces to the polynomial

$$\Delta(\lambda) = \lambda^2 + (\psi_1 - \psi_2 + \overline{\delta})\lambda + (\overline{\delta}\psi_1 + \psi_3 - \psi_1\psi_2) = 0\,. \tag{2.12}$$

Theorem 2.4. *When* $\tau = 0$, *the endemic equilibrium* $(\overline{x}_+, \overline{y}_+)$ *is locally asymptotically stable if, and only if,* $\psi_1 - \psi_2 + \overline{\delta} > 0$ *and* $\overline{\delta}\psi_1 + \psi_3 - \psi_1\psi_2 > 0$.

Proof. The proof is a consequence of a direct application of the Routh–Hurwitz criterion. □

Let $\lambda = i\omega$, $\omega \in \mathbb{R}^+$. Then the characteristic equation (2.10) yields

$$\begin{aligned}\Delta(i\omega) = &-\omega^2 + i(\psi_1 + \overline{\delta})\omega + \overline{\delta}\psi_1 + (\psi_3 - \psi_1\psi_2)\cos(\omega\tau) - i\,(\psi_3 - \psi_1\psi_2)\sin(\omega\tau)\\ &- i\omega\psi_2\cos(\omega\tau) - \omega\psi_2\sin(\omega\tau) = 0\end{aligned} \tag{2.13}$$

if, and only if,

$$\begin{cases}\omega\psi_2\sin(\omega\tau) + (\psi_1\psi_2 - \psi_3)\cos(\omega\tau) = \overline{\delta}\psi_1 - \omega^2\,,\\ (\psi_3 - \psi_1\psi_2)\sin(\omega\tau) + \omega\psi_2\cos(\omega\tau) = \left(\psi_1 + \overline{\delta}\right)\omega\,.\end{cases} \tag{2.14}$$

Solving the system (2.14) for $\cos(\omega\tau)$ and $\sin(\omega\tau)$ yields

$$\begin{cases}\sin(\omega\tau) = \frac{\omega\left(\psi_1\psi_3 + \overline{\delta}\psi_3 - \psi_1^2\psi_2 - \omega^2\psi_2\right)}{\omega^2\psi_2^2 + (\psi_1\psi_2 - \psi_3)^2}\,,\\ \cos(\omega\tau) = \frac{\overline{\delta}\omega^2\psi_2 + \overline{\delta}\psi_1^2\psi_2 - \overline{\delta}\psi_1\psi_2 + \omega^2\psi_3}{\omega^2\psi_2^2 + (\psi_1\psi_2 - \psi_3)^2}\,.\end{cases} \tag{2.15}$$

Squaring and adding the expressions in (2.15) gives the polynomial in ω:

$$\Phi(\omega) := \xi_6\omega^6 + \xi_4\omega^4 + \xi_2\omega^2 + \xi_0 = 0\,, \tag{2.16}$$

where

$$\begin{aligned}\xi_6 &:= \psi_2^2\,,\\ \xi_4 &:= \overline{\delta}^2\psi_2^2 + 2\psi_1^2\psi_2^2 - \psi_2^4 - 2\psi_1\psi_2\psi_3 + \psi_3^2\,,\\ \xi_2 &:= 2\sigma^2\psi_1^2\psi_2^2 + \psi_1^4\psi_2^2 - 2\psi_1^2\psi_2^4 - 2\overline{\delta}^2\psi_1\psi_2\psi_3\\ &\quad - 2\psi_1^3\psi_2\psi_3 + 4\psi_1\psi_2^3\psi_3 + \overline{\delta}^2\psi_3^2 + \psi_1^2\psi_3^2 - 2\psi_2^2\psi_3^2\,,\\ \xi_0 &:= \overline{\delta}^2\psi_1^4\psi_2^2 - \psi_1^4\psi_2^4 - 2\overline{\delta}^2\psi_1^3\psi_2\psi_3 + 4\psi_1^3\psi_2^3\psi_3\\ &\quad + \overline{\delta}^2\psi_1^2\psi_3^2 - 6\psi_1^2\psi_2^2\psi_3^2 + 4\psi_1\psi_2\psi_3^3 - \psi_3^4\,.\end{aligned} \tag{2.17}$$

Theorem 2.5. *If* $\xi_0 < 0$, *then the polynomial* (2.16) *has at least one positive real root.*

Proof. It is evident from (2.16) that $\Phi(0) = \xi_0$, and that $\lim_{\omega\to+\infty}\Phi(\omega) = +\infty$. Thus, there exists an $\omega^* \in (0, +\infty)$ such that $\Phi(\omega^*) = 0$. The result follows. □

Theorem 2.5 implies that the characteristic equation (2.10) possesses a pair of pure imaginary roots $\lambda = \pm i\omega^*$. For convenience, let us suppose that $z := \omega^2$ in the polynomial (2.16). Then, (2.16) is expressible in the form

$$\Phi(z) := \xi_6 z^3 + \xi_4 z^2 + \xi_2 z + \xi_0 = 0\,. \tag{2.18}$$

Theorem 2.6. *If $\xi_0 \geq 0$ and $\xi_2\xi_6 > 0$, then the polynomial (2.18) has no positive real roots.*

Proof. We note from (2.18) that

$$\Phi'(z) = 3\xi_6 z^2 + 2\xi_4 z + \xi_2 = 0 \tag{2.19}$$

if, and only if,

$$z_\pm = \frac{-\xi_4 \pm \sqrt{\xi_4^2 - 3\xi_2\xi_6}}{3\xi_6}\,. \tag{2.20}$$

If $\xi_2\xi_6 > 0$, then $\xi_4^2 - 3\xi_2\xi_6 < \xi_4^2$. This implies that $\sqrt{\xi_4^2 - 3\xi_2\xi_6} < \xi_4^2$, and so $-\xi_4 + \sqrt{\xi_4^2 - 3\xi_2\xi_6} < 0$. Consequently, it follows that $z_+ < 0$ and $z_- < 0$. We conclude that the polynomial (2.18) has no positive real roots. $\Phi(0) = \xi_0 > 0 \Longrightarrow$ (2.16) has no positive real roots. The result follows. □

We now attempt to characterise the local asymptotic stability of the endemic equilibrium $(\overline{x}_+, \overline{y}_+)$. We do so by recourse to Rouché's Theorem [16, p. 247, Theorem 9.17.3].

Theorem 2.7. *If $\psi_1 > 0$ and $|\psi_1\psi_2 - \psi_3| < \overline{\delta}\psi_1$, then the characteristic equation (2.10) has no roots with positive real part.*

Proof. A complete proof is given in the Appendix. □

Finally, a comment on the endemic equilibrium $(\overline{x}_-, \overline{y}_-)$. It is straightforward to establish that the characteristic equation associated with this equilibrium is of the form

$$\overline{\Delta}(\lambda) := \lambda^2 + (\overline{\psi}_1 + \overline{\delta})\lambda + \overline{\delta}\overline{\psi}_1 + (\overline{\psi}_3 - \lambda\overline{\psi}_2 - \overline{\psi}_1 \cdot \overline{\psi}_2)e^{-\lambda\tau} = 0\,, \tag{2.21}$$

where

$$\begin{cases} \overline{\psi}_1 := -\alpha + 2\alpha\beta\overline{y}_- + 2\overline{x}_- + 2\beta\overline{y}_-\,, \\ \overline{\psi}_2 := \omega(1 + \overline{y}_-)\,, \\ \overline{\psi}_3 := 2\omega\overline{x}_- \cdot \overline{y}_-\,. \end{cases} \tag{2.22}$$

The similarity between (2.10) and (2.21) is clear. Thus, the stability analysis of the equilibrium $(\overline{x}_-, \overline{y}_-)$ carries through in a manner analogous to that of $(\overline{x}_+, \overline{y}_+)$. The only difference is the definition of the parameters given in (2.22) and in (2.11).

3 Hopf bifurcation of $(\overline{x}_+, \overline{y}_+)$

We now formulate a local Hopf bifurcation theorem for the endemic equilibrium $(\overline{x}_+, \overline{y}_+)$, with τ as the bifurcation parameter. Let $\lambda = \lambda(\tau)$, and differentiate (2.10) with respect to τ to get

$$\frac{d\lambda}{d\tau} = \frac{\lambda\left(\psi_3 - \lambda\psi_2 - \psi_1\psi_2\right)e^{-\lambda\tau}}{2\lambda + \psi_2 + \overline{\delta} - \psi_2 e^{-\lambda\tau} - \tau\left(\psi_3 - \lambda\psi_2 - \psi_1\psi_2\right)e^{-\lambda\tau}}\,, \tag{3.1}$$

which leads to

$$\operatorname{Re}\left(\left.\frac{d\lambda}{d\tau}\right|_{\lambda=i\omega}\right) = \frac{\eta_1\chi_1 - \eta_2\chi_2}{\chi_1^2 + \chi_2^2}\,, \tag{3.2}$$

where

$$\begin{cases} \chi_1 := \overline{\delta} + \psi_2 - \psi_2\cos(\omega\tau) - \tau(\psi_3 - \psi_1\psi_2)\cos(\omega\tau) + \tau\omega\psi_2\sin(\omega\tau)\,, \\ \chi_2 := 2\omega + \psi_2\sin(\omega\tau) + \tau(\psi_3 - \psi_1\psi_2)\sin(\omega\tau) + \tau\omega\psi_2\cos(\omega\tau)\,, \\ \eta_1 := \omega^2\psi_2\cos(\omega\tau) + \omega(\psi_3 - \psi_1\psi_2)\sin(\omega\tau)\,, \\ \eta_2 := \omega^2\psi_2\sin(\omega\tau) - \omega(\psi_3 - \psi_1\psi_2)\cos(\omega\tau)\,. \end{cases} \tag{3.3}$$

Thus, we see from (3.2) that the usual transversality condition is satisfied if, and only if,

$$\begin{aligned} &\omega\left(\overline{\delta}\omega\psi_2 - 2\omega\psi_1\psi_2 + \omega\psi_2^2 + 2\omega\psi_3\right)\cos(\omega\tau) \\ &\qquad\neq \omega\left(\overline{\delta}\psi_1\psi_2 + 2\omega^2\psi_2 + \psi_1\psi_2^2 - \overline{\delta}\psi_3 - \psi_2\psi_3\right)\sin(\omega\tau)\,. \end{aligned} \tag{3.4}$$

Therefore, by continuity, $\operatorname{Re}(\lambda(\tau))$ becomes positive when $\tau > \tau^0$ and the equilibrium $(\overline{x}_+, \overline{y}_+)$ becomes unstable. A simple root Hopf bifurcation occurs as the time delay τ passes through the critical value τ^0, with

$$\tau^0 := \frac{1}{\omega_0}\cos^{-1}\left[\frac{\overline{\delta}\omega_0^2\psi_2 + \overline{\delta}\psi_1^2\psi_2 - \overline{\delta}\psi_1\psi_3 + \omega_0^2\psi_3}{\omega_0^2\psi_2^2 + (\psi_1\psi_2 - \psi_3)^2}\right]. \tag{3.5}$$

Let $\lambda(\tau) = \eta(\tau) + i\omega(\tau)$ be the root of (2.10) such that $\eta\left(\tau^0\right) = 0$ and $\omega\left(\tau^0\right) = \omega_0$. We obtain from equation (2.15) that

$$\tau^j = \frac{1}{\omega_0}\cos^{-1}\left[\frac{\overline{\delta}\omega_0^2\psi_2 + \overline{\delta}\psi_1^2\psi_2 - \overline{\delta}\psi_1\psi_3 + \omega_0^2\psi_3}{\omega_0^2\psi_2^2 + (\psi_1\psi_2 - \psi_3)^2}\right] + \frac{2j\pi}{\omega_0}\,, \qquad j = 0, 1, 2, \ldots \tag{3.6}$$

We arrive at the following result.

Theorem 3.1. *Suppose that*

(a) Theorem 2.4 and condition (3.4) hold, and that equation (2.16) has no positive real roots (at least for $0 < \tau \leq \widetilde{\tau}$, where $\widetilde{\tau} > \tau^0$). If either

(b) $\xi_0 < 0$, or

(c) $\xi_0 \geq 0$, $\xi_2\xi_6 < 0$, and $2(3 - \xi_4^2)\sqrt{\xi_4^2 - 3\xi_2\xi_6} \leq 9\xi_2\xi_4\xi_6 - 27\xi_0\xi_6^2 - 2\xi_4^2$

is satisfied, then the equilibrium $(\overline{x}_+, \overline{y}_+)$ of (1.2) with characteristic equation (2.10) is locally asymptotically stable when $\tau < \tau^0$ and unstable when $\tau^0 < \tau < \min\left\{\widetilde{\tau}, \tau^1\right\}$, where

$$\tau^0 := \frac{1}{\omega_0}\cos^{-1}\left[\frac{\overline{\delta}\omega_0^2\psi_2 + \overline{\delta}\psi_1^2\psi_2 - \overline{\delta}\psi_1\psi_3 + \omega_0^2\psi_3}{\omega_0^2\psi_2^2 + (\psi_1\psi_2 - \psi_3)^2}\right] \tag{3.7}$$

and

$$\tau^1 := \frac{1}{\omega_0}\cos^{-1}\left[\frac{\bar{\delta}\omega_0^2\psi_2 + \bar{\delta}\psi_1^2\psi_2 - \bar{\delta}\psi_1\psi_3 + \omega_0^2\psi_3}{\omega_0^2\psi_2^2 + (\psi_1\psi_2 - \psi_3)^2}\right] + \frac{2\pi}{\omega_0}\,. \tag{3.8}$$

When $\tau = \tau^0$, a simple root Hopf bifurcation occurs. That is, a family of periodic solutions bifurcates from $(\bar{x}_+, \bar{y}_+)$ as τ passes through the critical value τ^0.

In order to adequately describe the criticality of the Hopf bifurcation characterised in Theorem 3.1, we must first project the system (2.8) onto the centre manifold, which is tangent to the centre space at the origin. An in-depth analytic algorithm for carrying out this task is described in [7,8], for instance. It is important to note that the centre manifold is locally invariant, and is attractive to the flow of (2.8). The nonlinear system (2.8) is expressible as an abstract functional differential equation in the form [21,22]

$$\frac{d\mathbf{x}_t(\theta)}{dt} = \begin{cases} \frac{d\mathbf{x}_t(\theta)}{d\theta}, & -\tau \le \theta < 0\,, \\ \mathbf{L}\mathbf{x}_t + \mathbf{f}(\mathbf{x}_t)\,, & \theta = 0\,, \end{cases} \tag{3.9}$$

where $\mathbf{x}_t(\theta) := \mathbf{x}(t+\theta)$, $-\tau \le \theta \le 0$, $\mathcal{C} := C([-\tau, 0], \mathbb{R}^2)$, $\mathbf{L} : C \to \mathbb{R}^2$ is a linear operator, and $\mathbf{f} \in C^r(\mathcal{C}, \mathbb{R}^2)$, $r \ge 1$. By recourse to the Riesz representation theorem [20, Theorem 4.4-1, p. 227], the linear operator $\mathbf{L}$ can be represented by a Riemann–Stieltjes integral [21,22]

$$\mathbf{L}\phi = \int_{-\tau}^{0} [d\eta(\theta)]\phi(\theta)\,, \tag{3.10}$$

where $\eta : [-\tau, 0] \to \mathbb{R}$ is a function of bounded variation. Now, in relation to the system (2.8), we have that

$$\mathbf{L}\mathbf{x}_t := \begin{pmatrix} \sigma + W\bar{x}_+ \cdot \bar{y}_+ - \bar{\delta}\bar{x}_+ + W\bar{y}_+\tilde{x}(t-\tau) + W\bar{x}_+\tilde{y}(t-\tau) - \bar{\delta}\tilde{x}(t) \\ \left[\alpha\left(1 - \beta\bar{y}_+\right) - \alpha\beta\bar{y}_+ - \bar{x}_+\right]\tilde{y}(t) - \bar{y}_+\tilde{x}(t) + \alpha\left(1 - \beta\bar{y}_+\right)\bar{y}_+ - \bar{x}_+\bar{y}_+ \end{pmatrix}, \tag{3.11}$$

$$\mathbf{f}(\mathbf{x}(t), \mathbf{x}(t-\tau), \alpha, \beta, W, \sigma, \bar{\delta}) := \begin{pmatrix} W\tilde{x}_t(-\tau)\tilde{y}_t(-\tau) \\ -\alpha\beta\tilde{y}_t^2(0) - \tilde{x}_t(0)\tilde{y}_t(0) \end{pmatrix}, \tag{3.12}$$

and

$$\eta(\theta) := \begin{pmatrix} W\left(1 + \bar{y}_+\right)\delta(\theta+\tau) - \bar{\delta}\delta(\theta) & W\bar{x}_+\delta(\theta+\tau) \\ -\bar{y}_+\delta(\theta) & \left(\alpha - 2\alpha\beta\bar{y}_+ - \bar{x}_+\right)\delta(\theta) \end{pmatrix}, \tag{3.13}$$

where $\delta(x)$ is the Dirac distribution centred at the point $x = 0$. In the case of a simple Hopf bifurcation, the elements needed to write the finite-dimensional system of ordinary differential equations on the centre manifold are given by [7]

$$\boldsymbol{\Phi}(\theta) := (\boldsymbol{\phi}_1(\theta), \boldsymbol{\phi}_2(\theta))\,, \qquad B := \begin{pmatrix} i\omega & 0 \\ 0 & -i\omega \end{pmatrix}, \qquad \mathbf{z} := \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} \equiv \begin{pmatrix} z \\ \bar{z} \end{pmatrix}, \tag{3.14}$$

where

$$\boldsymbol{\phi}_1(\theta) := \begin{pmatrix} 1 \\ 1 \end{pmatrix} e^{i\omega\theta} \quad \text{and} \quad \boldsymbol{\phi}_2(\theta) := \begin{pmatrix} 1 \\ 1 \end{pmatrix} e^{-i\omega\theta}\,. \tag{3.15}$$

The bilinear form associated with the linear part of (3.9) is given by [21]

$$\langle \psi, \phi \rangle = \psi(0)\phi(0) - \int_{-\tau}^{0}\int_{0}^{\theta} \psi(\xi - \theta)[d\eta(\theta)]\phi(\xi)d\xi d\theta\,. \tag{3.16}$$

Using the bilinear form (3.16) leads to the matrix

$$\langle \mathbf{\Phi}^*, \mathbf{\Phi} \rangle = \begin{pmatrix} \langle \phi_1^*, \phi_1 \rangle & \langle \phi_1^*, \phi_2 \rangle \\ \langle \phi_2^*, \phi_1 \rangle & \langle \phi_2^*, \phi_2 \rangle \end{pmatrix}$$
$$= \begin{pmatrix} 2 + \frac{i}{\omega}\left[W\left(1+\overline{x}_+ + \overline{y}_+\right)\cos(\omega\tau) \right. & 2 + W\tau\left(1+\overline{x}_+ + \overline{y}_+\right)\cos(\omega\tau) \\ \left. + \left(\alpha - 2\alpha\beta\overline{y}_+ - \overline{x}_+ - \overline{\delta} - \overline{y}_+\right)\right] & +iW\tau\left(1+\overline{x}_+ + \overline{y}_+\right)\sin(\omega\tau) \\ & \\ 2 + W\tau\left(1+\overline{x}_+ + \overline{y}_+\right)\cos(\omega\tau) & 2 + \frac{i}{\omega}\left[W\left(1+\overline{x}_+ + \overline{y}_+\right)\cos(\omega\tau)\right. \\ -iW\tau\left(1+\overline{x}_+ + \overline{y}_+\right)\sin(\omega\tau) & \left. + \left(\alpha - 2\alpha\beta\overline{y}_+ - \overline{x}_+ - \overline{\delta} - \overline{y}_+\right)\right] \end{pmatrix}. \quad (3.17)$$

The basis for the adjoint linear problem, $\mathbf{\Psi}(s), s \in [0, \tau]$, is described by [7]

$$\mathbf{\Psi}(s) = \langle \mathbf{\Phi}^*(s), \mathbf{\Phi}(\theta) \rangle^{-1} \mathbf{\Phi}^*(s) \,,$$

and thus

$$\mathbf{\Psi}(0) = \langle \mathbf{\Phi}^*(0), \mathbf{\Phi}(\theta) \rangle^{-1} \mathbf{\Phi}^*(0) = \frac{1}{d_R^2 + d_I^2} \begin{pmatrix} \eta_{11} & \eta_{12} \\ \eta_{21} & \eta_{22} \end{pmatrix}, \quad (3.18)$$

where

$$\begin{aligned} \eta_{11} = \eta_{12} &:= 2d_R + \xi d_I + d_R\chi_1 - d_I\chi_2 + i\left(\xi d_R - 2d_I - d_R\chi_2 - d_I\chi_1\right), \\ \eta_{21} = \eta_{22} &:= d_R\chi_1 + d_I\chi_2 + 2d_R + \xi d_I + i\left(d_R\chi_2 - d_I\chi_1 + \xi d_R - 2d_I\right), \\ \xi &:= \frac{1}{\omega}\left[W\left(1+\overline{x}_+ + \overline{y}_+\right)\cos(\omega\tau) + \alpha - 2\alpha\beta\overline{y}_+ - \overline{x}_+ - \overline{\delta} - \overline{y}_+\right], \\ \chi_1 &:= -2 - W\tau\left(1+\overline{x}_+ + \overline{y}_+\right)\cos(\omega\tau)\,, \\ \chi_2 &:= W\tau\left(1+\overline{x}_+ + \overline{y}_+\right)\sin(\omega\tau)\,, \\ d_I &:= -\frac{1}{\omega^2}\left[-4\omega\alpha + 4\omega\overline{x}_+ + 4\omega\overline{y}_+ - 4\overline{\delta}\omega - 4W\omega\cos(\omega\tau)\right. \\ &\quad \left. + 8\alpha\beta\omega\overline{y}_+ - 4W\omega\overline{x}_+\cos(\omega\tau) - 4W\omega\overline{y}_+\cos(\omega\tau)\right], \end{aligned} \quad (3.19)$$

and

$$\begin{aligned} d_R := -\frac{1}{\omega^2}\Big[& 4W\tau\omega^2\cos(\omega\tau) - 4\alpha^2\beta\overline{y}_+ + 4\alpha^2\beta^2\overline{y}_+^2 + 4\alpha\beta\overline{y}_+^2 + 2W^2\overline{x}_+\overline{y}_+ cos^2(\omega\tau) \\ & + 2W\alpha\overline{x}_+\cos(\omega\tau) + 2W\alpha\overline{y}_+\cos(\omega\tau) - 2W\overline{x}_+\overline{\delta}\cos(\omega\tau) - 4W\overline{x}_+\overline{y}_+ \\ & - 2W\overline{y}_+\overline{\delta}\cos(\omega\tau) + 2W^2\tau^2\omega^2\overline{x}_+ + W^2\tau^2\omega^2\overline{y}_+^2 + W^2\tau^2\omega^2\overline{x}_+^2 \\ & + 2W^2\tau^2\omega^2\overline{y}_+ + W^2\tau^2\omega^2 + \overline{\delta}^2 + \overline{y}_+^2 + \alpha^2 + \overline{x}_+^2 - 2W\overline{x}_+^2\cos(\omega\tau) \\ & - 2W\overline{y}_+^2\cos(\omega\tau) - 2\alpha\overline{y}_+ - 2W\overline{\delta}\cos(\omega\tau) + 2\overline{x}_+\overline{y}_+ + 2\overline{\delta}\overline{y}_+ - 2\alpha\overline{x}_+ \\ & - 2\alpha\overline{\delta} + 2W^2\overline{y}_+\cos^2(\omega\tau) + 2W\alpha\cos(\omega\tau) + W^2\overline{x}_+^2\cos^2(\omega\tau) \\ & + W^2\overline{y}_+^2\cos^2(\omega\tau) + 2\overline{\delta}\overline{x}_+ + 2W^2\overline{x}_+\cos^2(\omega\tau) - 2W\overline{x}_+\cos(\omega\tau) \\ & - 2W\overline{y}_+\cos(\omega\tau) + 4W\tau\omega^2\overline{x}_+\cos(\omega\tau) + 4W\tau\omega^2\overline{y}_+\cos(\omega\tau) \\ & - 4W\alpha\beta\overline{y}_+\cos(\omega\tau) - 4W\alpha\beta\overline{y}_+^2\cos(\omega\tau) + 4\alpha\beta\overline{x}_+\overline{y}_+ + 4\alpha\beta\overline{y}_+\overline{\delta} \\ & + W^2\cos^2(\omega\tau) + 2W^2\tau^2\omega^2\overline{x}_+\overline{y}_+ - 4W\alpha\beta\overline{x}_+\overline{y}_+\Big]. \end{aligned} \quad (3.20)$$

The centre manifold system of ordinary differential equations is given by [7,8]

$$\mathbf{z}'(t) = B\mathbf{z}(t) + \mathbf{\Psi}(0)\mathbf{f}\left[\mathbf{\Phi}(\theta)\mathbf{z}(t) + \mathbf{u}_2(\theta)\mathbf{z}^2(t) + \mathbf{u}_3(\theta)\mathbf{z}^3(t) + \cdots\right], \tag{3.21}$$

where $z^2(t) \equiv \mathbf{z}(t)\mathbf{z}^{\mathsf{T}}(t)$, $\mathbf{z}^3(t) \equiv \mathbf{z}(t)\mathbf{z}^{\mathsf{T}}(t)\mathbf{z}(t)$, and the matrices $\mathbf{u}_j(\theta)$, $j = 2, 3, \ldots$, are coefficients of the higher order terms in the expansion, and these higher order terms are needed in order to carry out the local Hopf bifurcation analysis precisely because the lowest order nonlinear terms in the right hand side of (2.8) are at most quadratic. We denote the matrices as

$$\mathbf{u}_2(\theta) := \begin{pmatrix} u_{211}(\theta) & u_{212}(\theta) & u_{213}(\theta) \\ u_{221}(\theta) & u_{222}(\theta) & u_{223}(\theta) \end{pmatrix} \quad \text{and} \quad \mathbf{u}_3(\theta) := \begin{pmatrix} u_{311}(\theta) & u_{312}(\theta) \\ u_{321}(\theta) & u_{322}(\theta) \end{pmatrix}, \tag{3.22}$$

and note further that

$$\mathbf{z}^2 := \begin{pmatrix} z_1^2 \\ z_1 z_2 \\ z_2^2 \end{pmatrix} \quad \text{and} \quad \mathbf{z}^3 := \begin{pmatrix} z_1^3 + z_1 z_2^2 \\ z_1^2 z_2 + z_2^3 \end{pmatrix}. \tag{3.23}$$

Let us denote

$$\mathbf{x}_t(\theta) = \mathbf{\Phi}(\theta)\mathbf{z}(t) + \mathbf{u}_2(\theta)\mathbf{z}^2(t) + \mathbf{u}_3(\theta)\mathbf{z}^3(t) + \cdots, \tag{3.24}$$

which can be expanded to the form

$$\begin{aligned} \mathbf{x}_t(\theta) = \boldsymbol{\phi}_1(\theta)z_1(t) + \boldsymbol{\phi}_2(\theta)z_2(t) &+ \begin{pmatrix} u_{211}(\theta)z_1^2 + u_{212}(\theta)z_1z_2 + u_{213}(\theta)z_2^2 \\ u_{221}(\theta)z_1^2 + u_{222}(\theta)z_1z_2 + u_{223}(\theta)z_2^2 \end{pmatrix} \\ &+ \begin{pmatrix} u_{311}(\theta)\left(z_1^3 + z_1z_2^2\right) + u_{312}(\theta)\left(z_1^2z_2 + z_2^3\right) \\ u_{321}(\theta)\left(z_1^3 + z_1z_2^2\right) + u_{322}(\theta)\left(z_1^2z_2 + z_2^3\right) \end{pmatrix} + \cdots \end{aligned} \tag{3.25}$$

Using the expansion (3.25) and the second part of (3.9) yields

$$\begin{aligned} &\boldsymbol{\phi}_1(0)z_1'(t) + \boldsymbol{\phi}_2(0)z_2'(t) \\ &\quad + \begin{pmatrix} 2u_{211}(0)z_1(t)z_1'(t) + u_{212}(0)z_1'(t)z_2(t) + u_{212}(0)z_1(t)z_2'(t) + 2u_{213}(0)z_2(t)z_2'(t) \\ 2u_{221}(0)z_1(t)z_1'(t) + u_{222}(0)z_1'(t)z_2(t) + u_{222}(0)z_1(t)z_2'(t) + 2u_{223}(0)z_2(t)z_2'(t) \end{pmatrix} \\ &\quad + \begin{pmatrix} u_{311}(0)\left(3z_1^2(t)z_1'(t) + z_1'(t)z_2^2(t) + 2z_1(t)z_2(t)z_2'(t)\right) + u_{312}(0)\left(2z_1(t)z_1'(t)z_2(t) + z_1^2(t)z_2'(t) + 3z_2^2(t)z_2'(t)\right) \\ u_{321}(0)\left(3z_1^2(t)z_1'(t) + z_1'(t)z_2^2(t) + 2z_1(t)z_2(t)z_2'(t)\right) + u_{322}(0)\left(2z_1(t)z_1'(t)z_2(t) + z_1^2(t)z_2'(t) + 3z_2^2(t)z_2'(t)\right) \end{pmatrix} \\ &= \begin{pmatrix} -\overline{\delta}\widetilde{x}_t(0) + W\overline{y}_+\widetilde{x}_t(-\tau) + W\overline{x}_+\widetilde{y}_t(-\tau) \\ -\overline{y}_+\widetilde{x}_t(0) + \left[\alpha(1-2\beta\overline{y}_+) - \overline{x}_+\right]\widetilde{y}_t(0) \end{pmatrix} + \begin{pmatrix} W\widetilde{x}_t(-\tau)\widetilde{y}_t(-\tau) \\ -\alpha\beta\widetilde{y}_t^2(0) - \widetilde{x}_t(0)\widetilde{y}_t(0) \end{pmatrix}. \end{aligned} \tag{3.26}$$

Equating coefficients of $z_j'(t)$, $j = 1, 2$, in (3.26) gives

$$\begin{aligned} \boldsymbol{\phi}_1(0) &+ \begin{pmatrix} 2u_{211}(0)z_1(t) + u_{212}(0)z_2(t) \\ 2u_{221}(0)z_1(t) + u_{222}(0)z_2(t) \end{pmatrix} \\ &+ \begin{pmatrix} u_{311}(0)(3z_1^2(t) + z_2^2(t)) + 2u_{312}(0)z_1(t)z_2(t) \\ u_{321}(0)(3z_1^2(t) + z_2^2(t)) + 2u_{322}(0)z_1(t)z_2(t) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \end{aligned} \tag{3.27}$$

and

$$\begin{aligned} \boldsymbol{\phi}_2(0) &+ \begin{pmatrix} u_{212}(0)z_1(t) + 2u_{213}(0)z_2(t) \\ u_{222}(0)z_1(t) + 2u_{223}(0)z_2(t) \end{pmatrix} \\ &+ \begin{pmatrix} 2u_{311}(0)z_1(t)z_2(t) + u_{312}(0)(z_1^2(t) + 3z_2^2(t)) \\ 2u_{321}(0)z_1(t)z_2(t) + u_{322}(0)(z_1^2(t) + 3z_2^2(t)) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \end{aligned} \tag{3.28}$$

Consequently, we obtain the following initial conditions from (3.27) and (3.28).

$$\begin{cases} 1+2u_{211}(0)z_1(t)+u_{212}(0)z_2(t)+u_{311}(0)(3z_1^2(t)+z_2^2(t))+2u_{312}(0)z_1(t)z_2(t)=0, \\ 1+2u_{221}(0)z_1(t)+u_{222}(0)z_2(t)+u_{321}(0)(3z_1^2(t)+z_2^2(t))+2u_{322}(0)z_1(t)z_2(t)=0, \\ 1+2u_{212}(0)z_1(t)+2u_{213}(0)z_2(t)+2u_{311}(0)z_1(t)z_2(t)+u_{312}(0)(z_1^2(t)+3z_2^2(t))=0, \\ 1+2u_{222}(0)z_1(t)+2u_{223}(0)z_2(t)+2u_{321}(0)z_1(t)z_2(t)+u_{322}(0)(z_1^2(t)+3z_2^2(t))=0. \end{cases} \tag{3.29}$$

Next, when $\theta = 0$, we note that

$$\mathbf{z}'(t) = B\mathbf{z}(t) \Longrightarrow \begin{pmatrix} z_1'(t) \\ z_2'(t) \end{pmatrix} = \begin{pmatrix} i\omega z_1(t) \\ -i\omega z_2(t) \end{pmatrix}. \tag{3.30}$$

From the first part of (3.9), we obtain the equation

$$\begin{aligned} &\boldsymbol{\phi}_1(\theta)z_1'(t)+\boldsymbol{\phi}_2(\theta)z_2'(t) \\ &\quad+\begin{pmatrix} 2u_{211}(\theta)z_1(t)z_1'(t)+u_{212}(\theta)z_1'(t)z_2(t)+u_{212}(\theta)z_1(t)z_2'(t)+2u_{213}(\theta)z_2(t)z_2'(t) \\ 2u_{221}(\theta)z_1(t)z_1'(t)+u_{222}(\theta)z_1'(t)z_2(t)+u_{222}(\theta)z_1(t)z_2'(t)+2u_{223}(\theta)z_2(t)z_2'(t) \end{pmatrix} \\ &\quad+\begin{pmatrix} u_{311}(\theta)\big(3z_1^2(t)z_1'(t)+z_1'(t)z_2^2(t)+2z_1(t)z_2(t)z_2'(t)\big)+u_{312}(\theta)\big(2z_1(t)z_1'(t)z_2(t)+z_1^2(t)z_2'(t)+3z_2^2(t)z_2'(t)\big) \\ u_{321}(\theta)\big(3z_1^2(t)z_1'(t)+z_1'(t)z_2^2(t)+2z_1(t)z_2(t)z_2'(t)\big)+u_{322}(\theta)\big(2z_1(t)z_1'(t)z_2(t)+z_1^2(t)z_2'(t)+3z_2^2(t)z_2'(t)\big) \end{pmatrix} \\ &=\boldsymbol{\phi}_1'(\theta)z_1(t)+\boldsymbol{\phi}_2'(\theta)z_2(t) \\ &\quad+\begin{pmatrix} u_{211}'(\theta)z_1^2(t)+u_{212}'(\theta)z_1(t)z_2(t)+u_{213}'(\theta)z_2^2(t) \\ u_{221}'(\theta)z_1^2(t)+u_{222}'(\theta)z_1(t)z_2(t)+u_{223}'(\theta)z_2^2(t) \end{pmatrix} \\ &\quad+\begin{pmatrix} u_{311}'(\theta)\big(z_1^3(t)+z_1(t)z_2^2(t)\big)+u_{312}'(\theta)\big(z_1^2(t)z_2(t)+z_2^3(t)\big) \\ u_{321}'(\theta)\big(z_1^3(t)+z_1(t)z_2^2(t)\big)+u_{322}'(\theta)\big(z_1^2(t)z_2(t)+z_2^3(t)\big) \end{pmatrix}. \end{aligned} \tag{3.31}$$

Substituting (3.30) into (3.31) gives the slightly simplified equation

$$\begin{aligned} &i\omega\boldsymbol{\phi}_1(\theta)z_1(t)-i\omega\boldsymbol{\phi}_2(\theta)z_2(t) \\ &\quad+\begin{pmatrix} 2i\omega u_{211}(\theta)z_1^2(t)-2i\omega u_{213}(\theta)z_2^2(t) \\ 2i\omega u_{221}(\theta)z_1^2(t)-2i\omega u_{223}(\theta)z_2^2(t) \end{pmatrix} \\ &\quad+\begin{pmatrix} u_{311}(\theta)\,\big(3i\omega z_1^3(t)-i\omega z_1(t)z_2^2(t)\big)+u_{312}(\theta)\,\big(i\omega z_1^2(t)z_2(t)-3i\omega z_2^3(t)\big) \\ u_{321}(\theta)\,\big(3i\omega z_1^3(t)-i\omega z_1(t)z_2^2(t)\big)+u_{322}(\theta)\,\big(i\omega z_1^2(t)z_2(t)-3i\omega z_2^3(t)\big) \end{pmatrix} \\ &=i\omega\boldsymbol{\phi}_1(\theta)z_1(t)-i\omega\boldsymbol{\phi}_2(\theta)z_2(t) \\ &\quad+\begin{pmatrix} u_{211}'(\theta)z_1^2(t)+u_{212}'(\theta)z_1(t)z_2(t)+u_{213}'(\theta)z_2^2(t) \\ u_{221}'(\theta)z_1^2(t)+u_{222}'(\theta)z_1(t)z_2(t)+u_{223}'(\theta)z_2^2(t) \end{pmatrix} \\ &\quad+\begin{pmatrix} u_{311}'(\theta)\,\big(z_1^3(t)+z_1(t)z_2^2(t)\big)+u_{312}'(\theta)\,\big(z_1^2(t)z_2(t)+z_2^3(t)\big) \\ u_{321}'(\theta)\,\big(z_1^3(t)+z_1(t)z_2^2(t)\big)+u_{322}'(\theta)\,\big(z_1^2(t)z_2(t)+z_2^3(t)\big) \end{pmatrix}. \end{aligned} \tag{3.32}$$

Equating coefficients of corresponding terms in (3.32) yields the following uncoupled system of ordinary differential equations

$$
\begin{aligned}
u'_{211}(\theta) &= 2i\omega u_{211}(\theta)\,, \\
u'_{212}(\theta) &= 0\,, \\
u'_{213}(\theta) &= -2i\omega u_{213}(\theta)\,, \\
u'_{221}(\theta) &= 2i\omega u_{221}(\theta)\,, \\
u'_{222}(\theta) &= 0\,, \\
u'_{223}(\theta) &= -2i\omega u_{223}(\theta)\,, \\
u'_{311}(\theta) &= i\omega u_{311}(\theta)\,, \\
u'_{312}(\theta) &= -i\omega u_{312}(\theta)\,, \\
u'_{321}(\theta) &= i\omega u_{312}(\theta)\,, \\
u'_{322}(\theta) &= -i\omega u_{322}(\theta)\,,
\end{aligned}
\tag{3.33}
$$

which is easily solved to give:

$$
\begin{aligned}
u_{211}(\theta) &= c_{211}e^{2i\omega\theta}\,, \\
u_{212}(\theta) &= c_{212}\,, \\
u_{213}(\theta) &= c_{213}e^{-2i\omega\theta}\,, \\
u_{221}(\theta) &= c_{221}e^{2i\omega\theta}\,, \\
u_{222}(\theta) &= c_{222}\,, \\
u_{223}(\theta) &= c_{223}e^{-2i\omega\theta}\,, \\
u_{311}(\theta) &= c_{311}e^{i\omega\theta}\,, \\
u_{312}(\theta) &= c_{312}e^{-i\omega\theta}\,, \\
u_{312}(\theta) &= c_{312}e^{i\omega\theta}\,, \\
u_{322}(\theta) &= c_{322}e^{-i\omega\theta}\,,
\end{aligned}
\tag{3.34}
$$

where $c_{211}, \dots, c_{322}$ are yet-to-be-determined constants of integration. We now express the set of initial conditions (3.29) in terms of the constants of integration $c_{211}, \dots, c_{322}$ to get:

$$
\begin{cases}
1 + 2c_{211}z_1(t) + c_{212}(0)z_2(t) + c_{311}(3z_1^2(t) + z_2^2(t)) + 2c_{312}z_1(t)z_2(t) = 0\,, \\
1 + 2c_{221}z_1(t) + c_{222}z_2(t) + c_{321}(3z_1^2(t) + z_2^2(t)) + 2c_{322}z_1(t)z_2(t) = 0\,, \\
1 + 2c_{212}z_1(t) + 2c_{213}z_2(t) + 2c_{311}z_1(t)z_2(t) + c_{312}(z_1^2(t) + 3z_2^2(t)) = 0\,, \\
1 + 2c_{222}z_1(t) + 2c_{223}z_2(t) + 2c_{321}z_1(t)z_2(t) + c_{322}(z_1^2(t) + 3z_2^2(t)) = 0\,.
\end{cases}
\tag{3.35}
$$

We solve the system (3.35) for the constants of integration $c_{211}, \dots, c_{322}$, thus:

$$
\begin{aligned}
c_{223} &= c_{311} = c_{312} = c_{321} = c_{322} = c_{213} = 1\,, \\
c_{211} &= c_{221} = \frac{-3z_1^3 + z_1z_2^2 - z_1^2z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2}{2z_1^2}\,, \\
c_{212} &= c_{222} = -\left(\frac{2z_1z_2 + z_2^2 + 3z_1^2 + 2z_2 + 1}{z_1}\right), \\
c_{221} &= c_{211} = \frac{-3z_1^3 + z_1z_2^2 - z_1^2z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2}{2z_1^2}\,, \\
c_{222} &= c_{212} = -\left(\frac{2z_1z_2 + z_1^2 + 3z_2^2 + 2z_2 + 1}{z_1}\right),
\end{aligned}
\tag{3.36}
$$

where $c_{223}, c_{311}, c_{312}, c_{321}, c_{322}, c_{213}$ are free variables all set to 1, without loss of generality. Now, substituting (3.36) into (3.34) gives us

$$\begin{aligned}
u_{211}(\theta) &= \left(\frac{-3z_1^3 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2}{2z_1^2}\right) e^{2i\omega\theta}\,, \\
u_{212}(\theta) &= -\left(\frac{2z_1 z_2 + z_2^2 + 3z_1^2 + 2z_2 + 1}{z_1}\right), \\
u_{213}(\theta) &= e^{-2i\omega\theta}\,, \\
u_{221}(\theta) &= \left(\frac{-3z_1^3 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2}{2z_1^2}\right) e^{2i\omega\theta}\,, \\
u_{222}(\theta) &= -\left(\frac{2z_1 z_2 + z_2^2 + 3z_1^2 + 2z_2 + 1}{z_1}\right), \\
u_{223}(\theta) &= e^{-2i\omega\theta}\,, \\
u_{311}(\theta) &= e^{i\omega\theta}\,, \\
u_{312}(\theta) &= e^{-i\omega\theta}\,, \\
u_{321}(\theta) &= e^{i\omega\theta}\,, \\
u_{322}(\theta) &= e^{-i\omega\theta}\,.
\end{aligned} \tag{3.37}$$

We note from (3.14) that

$$\mathbf{\Phi}(\theta)\mathbf{z}(t) = \begin{pmatrix} z_1(t)e^{i\omega\theta} + z_2(t)e^{-i\omega\theta} \\ z_1(t)e^{i\omega\theta} + z_2(t)e^{-i\omega\theta} \end{pmatrix}. \tag{3.38}$$

From (3.22) and (3.23), we have that

$$\begin{aligned}
\mathbf{u}_2(\theta)\mathbf{z}^2(t) &= \begin{pmatrix} u_{211}(\theta)z_1^2(t) + u_{212}(\theta)z_1(t)z_2(t) + u_{213}(\theta)z_2^2(t) \\ u_{221}(\theta)z_1^2(t) + u_{222}(\theta)z_1(t)z_2(t) + u_{223}(\theta)z_2^2(t) \end{pmatrix} \\
&= \begin{pmatrix} \frac{1}{2}\left(-3z_1^3 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) e^{2i\omega\theta} \\ -\left(2z_1 z_2 + z_2^2 + 3z_1^2 + 2z_2 + 1\right) z_2 + z_2^2 e^{-2i\omega\theta} \\ \\ \frac{1}{2}\left(-3z_1^3 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) e^{2i\omega\theta} \\ -\left(2z_1 z_2 + z_1^2 + 3z_2^2 + 2z_2 + 1\right) z_2 + z_2^2 e^{-2i\omega\theta} \end{pmatrix},
\end{aligned} \tag{3.39}$$

and

$$\begin{aligned}
\mathbf{u}_3(\theta)\mathbf{z}^3(t) &= \begin{pmatrix} u_{311}(\theta)\left(z_1^3 + z_1 z_2^2\right) + u_{312}(\theta)\left(z_1^2 z_2 + z_2^3\right) \\ u_{321}(\theta)\left(z_1^3 + z_1 z_2^2\right) + u_{322}(\theta)\left(z_1^2 z_2 + z_2^3\right) \end{pmatrix} \\
&= \begin{pmatrix} \left(z_1^3 + z_1 z_2^2\right) e^{i\omega\theta} + \left(z_1^2 z_2 + z_2^3\right) e^{-i\omega\theta} \\ \left(z_1^3 + z_1 z_2^2\right) e^{i\omega\theta} + \left(z_1^2 z_2 + z_2^3\right) e^{-i\omega\theta} \end{pmatrix}.
\end{aligned} \tag{3.40}$$

The expressions (3.12), (3.38), (3.39), and (3.40) lead to the following approximation of the nonlinearity $\mathbf{f}$:

$$\mathbf{f}\left(\mathbf{\Phi}(\theta)\mathbf{z} + \mathbf{u}_2(\theta)\mathbf{z}^2 + \mathbf{u}_3(\theta)\mathbf{z}^3 + \cdots\right) = \begin{pmatrix} f_1 \\ f_2 \end{pmatrix} + \cdots\,, \tag{3.41}$$

where

$$
\begin{aligned}
f_1 := W\Big[& z_1 e^{-i\omega\tau} + z_2 e^{i\omega\tau} + \frac{1}{2}\left(-3z_1^3 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) e^{-2i\omega\tau} \\
& - \left(2z_1 z_2 + z_2^2 + 3z_1^2 + 2z_2 + 1\right) z_2 + z_2^2 e^{2i\omega\tau} \\
& + \left(z_1^3 + z_1 z_2^2\right) e^{-i\omega\tau} + \left(z_1^2 z_2 + z_2^3\right) e^{i\omega\tau}\Big] \\
\times \Big[& z_1 e^{-i\omega\tau} + z_2 e^{i\omega\tau} + \frac{1}{2}\left(-3z_1^3 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) e^{-2i\omega\tau} \\
& - \left(2z_1 z_2 + z_1^2 + 3z_2^2 + 2z_2 + 1\right) z_2 + z_2^2 e^{2i\omega\tau} \\
& + \left(z_1^3 + z_1 z_2^2\right) e^{-i\omega\tau} + \left(z_1^2 z_2 + z_2^3\right) e^{i\omega\tau}\Big],
\end{aligned}
\tag{3.42}
$$

and

$$
\begin{aligned}
f_2 := -\alpha\beta \Big[& z_1 + z_2 + \frac{1}{2}\left(-3z_1^2 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) \\
& - \left(2z_1 z_2 + z_1^2 + 3z_2^2 + 2z_2 + 1\right) z_2 + z_2^2\Big]^2 \\
- \Big[& z_1 + z_2 + \frac{1}{2}\left(-3z_1^2 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) \\
& - \left(2z_1 z_2 + z_2^2 + 3z_1^2 + 2z_2 + 1\right) z_2 + z_2^2\Big] \\
\times \Big[& z_1 + z_2 + \frac{1}{2}\left(-3z_1^2 + z_1 z_2^2 - z_1^2 z_2 + 3z_2^3 + 2z_2^2 - z_1 + z_2\right) \\
& - \left(2z_1 z_2 + z_1^2 + 3z_2^2 + 2z_2 + 1\right) z_2 + z_2^2\Big].
\end{aligned}
\tag{3.43}
$$

Now, substituting (3.14), (3.38), (3.12), (3.42), and (3.43) into (3.21), and setting $z_1 := x + iy$ and $z_2 = \bar{z}_1 := x - iy$, gives us the dynamical system defined on the centre manifold:

$$
\begin{cases}
x' = -\omega y + F_{1111}x^3 + F_{1112}x^2 y + F_{1122}xy^2 + F_{1222}y^3 , \\
y' = \omega x + F_{2111}x^3 + F_{2112}x^2 y + F_{2122}xy^2 + F_{2222}y^3 ,
\end{cases}
\tag{3.44}
$$

where the real coefficients $F_{1111}, F_{1112}, F_{1122}, F_{1222}, F_{2111}, F_{2112}, F_{2122}, F_{2222}$ are extracted using the symbolic computation algebra package MAPLE, and are too lengthy to include here. To characterise the criticality of the Hopf bifurcation described in Theorem 3.1, we consider the so-called Poincaré–Lyapunov constant given by the formula [9,19]

$$
a := \frac{3F_{1111} + F_{1122} + F_{2112} + 3F_{2222}}{8} . \tag{3.45}
$$

The MAPLE worksheet used to extract these coefficients, calculate, and sketch the Poincaré-Lyapunov constant (3.45) as a function of the time delay τ is given in the Appendix. As is well-known [7,9], if $a < 0$, then the Hopf bifurcation is supercritical – giving rise to a stable limit cycle. On the other hand, if $a > 0$, then the Hopf bifurcation is subcritical, and generates an unstable limit cycle. Figure 3.1 gives a sketch of a graph of the Poincaré–Lyapunov constant (3.45) parameterised by the immune response time delay τ, with the rest of the model parameters held constant.

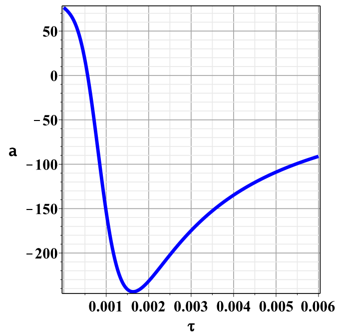

Figure 3.1: Change in criticality of Hopf bifurcation of the endemic equilibrium $(\overline{x}_+, \overline{y}_+)$ as depicted by a graph of the Poincaré-Lyapunov constant (3.45) parametrised by the immune response time delay τ. The rest of the model parameters are fixed as follows [1]: $\beta = 0.002$, $\overline{\delta} = 0.3743$, $\sigma = 0.1181$, $W = (\theta - m)/n$, $\theta = 3.422 \times 10^{-11}$, $\alpha = 2.636$, $m = 3.422 \times 10^{-5}$, $\omega = 2.25$, and $n = 1.101 \times 10^{-7}$.

Appendix

We begin by giving a full proof of Theorem 2.7.

Proof. In (2.10), let $h_1(\lambda) := \lambda^2 + (\psi_2 + \overline{\delta})\lambda + \overline{\delta}\psi_1$ and $h_2(\lambda) := (\psi_3 - \lambda\psi_2 - \psi_1\psi_2)e^{-\lambda\tau}$. Consider the contour C in the complex plane given by $C := C_1 \cup C_2$, where

$$\begin{cases} C_1 : & \lambda = Re^{i\theta} \ , \ -\frac{\pi}{2} \leq \theta \leq \frac{\pi}{2} \\ C_2 : & \lambda = iy \ , \ -R \leq y \leq R \ , \quad R \in \mathbb{R}^+ \ . \end{cases} \tag{3.46}$$

On the segment C_1, we have that

$$\begin{aligned} h_2(\lambda) &= h_2\left(Re^{i\theta}\right) \\ &= \left(\psi_3 - \psi_2 Re^{i\theta} - \psi_1\psi_2\right) e^{-\tau Re^{i\theta}} \\ &= e^{-\tau R\cos\theta}\big[(\psi_3 - \psi_2 R\cos\theta - \psi_1\psi_2)\cos(\tau R\sin\theta) - \psi_2 R\sin\theta\sin(\tau R\sin\theta) \\ &\quad - i\left\{\psi_2 R\sin\theta\cos(\tau R\sin\theta) + (\psi_3 - \psi_2 R\cos\theta - \psi_1\psi_2)\sin(\tau R\sin\theta)\right\}\big] \ . \end{aligned} \tag{3.47}$$

Consequently, we obtain

$$\begin{aligned} |h_2(\lambda)| &= e^{-\tau R\cos\theta}\sqrt{\psi_1^2\psi_2^2 + \psi_2^2 R^2 + \psi_3^2 - 2\psi_1\psi_2\psi_3 + 2(\psi_1\psi_2 - \psi_3)\psi_2 R\cos\theta} \\ &\leq \sqrt{(|\psi_1\psi_2| + |\psi_3|)^2 + |\psi_1\psi_2 - \psi_3|^2} \ . \end{aligned} \tag{3.48}$$

Analogously, on the segment C_1, we have that

$$h_1(\lambda) = Q_R + iQ_I \ , \tag{3.49}$$

where

$$\begin{aligned} Q_R &:= R^2\cos(2\theta) + R(\psi_2 + \overline{\delta})\cos\theta + \overline{\delta}\psi_1 \ , \\ Q_I &:= R^2\sin(2\theta) + R(\psi_2 + \overline{\delta})\sin\theta \ . \end{aligned} \tag{3.50}$$

Hence, we obtain

$$
\begin{aligned}
|h_1(\lambda)| &= \sqrt{Q_R^2 + Q_I^2} \\
&\geq \sqrt{2R\bar{\delta}} \cdot \sqrt{(R+\bar{\delta}\psi_2)(|\psi_1|+R) + |\psi_1|(\psi_2+R)}
\end{aligned}
\tag{3.51}
$$

From the inequalities (3.48) and (3.51), it is clear that for R sufficiently large, $|h_1(\lambda)| > |h_2(\lambda)|$ on the contour segment C_1 of C.

We now turn our attention to the segment C_2 of the contour C. We obtain

$$
\begin{aligned}
h_1(\lambda) &= h_1(iy) \\
&= (\bar{\delta}\psi_1 - y^2) + iy(\psi_1 + \bar{\delta}) \ .
\end{aligned}
\tag{3.52}
$$

Thus, we have that

$$
\begin{aligned}
|h_1(\lambda)| &= \sqrt{y^4 + (\bar{\delta}^2 + \psi_1^2)y^2 + \bar{\delta}^2\psi_1^2} \\
&\geq \bar{\delta}\psi_1 \ .
\end{aligned}
\tag{3.53}
$$

Similarly, we see that

$$
\begin{aligned}
h_2(\lambda) &= h_2(iy) \\
&= [(\psi_3 - \psi_1\psi_2)\cos(y\tau) - y\psi_2\sin(y\tau)] - i\,[(\psi_3 - \psi_1\psi_2)\sin(y\tau) + y\psi_2\cos(y\tau)] \ ,
\end{aligned}
\tag{3.54}
$$

and

$$
\begin{aligned}
|h_2(\lambda)| &= \sqrt{\psi_1^2\psi_2^2 + \psi_2^2 y^2 - 2\psi_1\psi_2\psi_3 + \psi_3^2} \\
&= \sqrt{\psi_1^2\psi_2^2 - (2\psi_1\psi_2\psi_3 - \psi_2^2 y^2) + \psi_3^2} \\
&\leq \sqrt{\psi_1^2\psi_2^2 - 2\psi_1\psi_2\psi_3 + \psi_3^2} \\
&= |\psi_1\psi_2 - \psi_3| \ .
\end{aligned}
\tag{3.55}
$$

Therefore, if follows from (3.53) and (3.55) that if $|\psi_1\psi_2 - \psi_3| < \bar{\delta}\psi_1$, then $|h_1(\lambda)| > |h_2(\lambda)|$ on the segment C_2 of the contour C. In addition, we do see that if $\psi_1\psi_2 \neq \psi_3$ or $\psi_1 \neq 0$, then neither $h_1(\lambda)$ nor $h_2(\lambda)$ vanishes anywhere on C. Thus, by Rouché's Theorem [16, p. 247, Theorem 9.17.3], if $|\psi_1\psi_2 - \psi_3| < \bar{\delta}\psi_1$ and R is sufficiently large, then $h_1(\lambda)$ and $\Delta(\lambda) = h_1(\lambda) + h_2(\lambda)$ have the same number of zeroes inside C. In the limit $R \to +\infty$, $h_1(\lambda)$ and $\Delta(\lambda)$ have the same number of zeroes with $\mathrm{Re}(\lambda) > 0$. But $h_1(\lambda) = \lambda^2 + (\psi_1 + \bar{\delta})\lambda + \bar{\delta}\psi_1$ has exactly two zeroes at $\lambda_+ := \frac{-(\psi_1+\bar{\delta})+|\psi_1-\bar{\delta}|}{2} < 0$ and $\lambda_- := \frac{-(\psi_1+\bar{\delta})-|\psi_1-\bar{\delta}|}{2} < 0$. This completes the proof. □

We now give a sample MAPLE worksheet that was employed in the calculation and plotting of the Poincaré–Lyapunov constant shown in (3.45), and depicted in Figure 3.1.

```
>E11:=expand(evalc(W*(z1*exp(-I*omega*tau)+z2*exp(I*omega*tau)+(1/2*(-3*z1^3-z1^2*z2
                    +z1*z2^2+3*z2^3+2*z2^2-z1+z2))*exp(-(2*I)*omega*tau)-(3*z1^2+2*z1
                    *z2+z2^2+2*z2+1)*z2+z2^2*exp((2*I)*omega*tau)+(z1^3+z1*z2^2)
                    *exp(-I*omega*tau)+(z1^2*z2+z2^3)*exp(I*omega*tau))
                    *(z1*exp(-I*omega*tau)+z2*exp(I*omega*tau)+(1/2*(-3*z1^3-z1^2*z2
                    +z1*z2^2+3*z2^3+2*z2^2-z1+z2))*exp(-(2*I)*omega*tau)-(z1^2+2*z1*z2
                    +3*z2^2+2*z2+1)*z2+z2^2*exp((2*I)*omega*tau)+(z1^3+z1*z2^2)
```

```
                  *exp(-I*omega*tau)+(z1^2*z2+z2^3)*exp(I*omega*tau)))):
> E12 := expand(-alpha*beta*(z1+z2+1/2*(-3*z1^3-z1^2*z2+z1*z2^2+3*z2^3+2*z2^2-z1+z2)
               -(z1^2+2*z1*z2+3*z2^2+2*z2+1)*z2+z2^2)^2-(z1+z2+1/2*(-3*z1^3-z1^2*z2
               +z1*z2^2+3*z2^3+2*z2^2-z1+z2)-(3*z1^2+2*z1*z2+z2^2+2*z2+1)*z2+z2^2)
               *(z1+(1/2)*z2*(-3*z1^3-z1^2*z2+z1*z2^2+3*z2^3+2*z2^2-z1+z2)-(z1^2
               +2*z1*z2+3*z2^2+2*z2+1)*z2+z2^2)):
>d_R := -(2*W^2*x*cos(omega*tau)^2+W^2*y^2*cos(omega*tau)^2-2*W*x*cos(omega*tau)
        -2*W*y*cos(omega*tau)-2*alpha*y+4*W*tau*x*omega^2*cos(omega*tau)
        +4*W*tau*y*omega^2*cos(omega*tau)-4*W*alpha*beta*y*cos(omega*tau)-4*W*y^2
        *alpha*beta*cos(omega*tau)+2*x*y+2*delta*y-2*alpha*x-2*alpha*delta+2*x*delta
        -4*W*x*alpha*beta*y*cos(omega*tau)+2*W*alpha*cos(omega*tau)+W^2*x^2
        *cos(omega*tau)^2+2*W^2*y*cos(omega*tau)^2-2*W*x^2*cos(omega*tau)-2*W*y^2
        *cos(omega*tau)+W^2*tau^2*omega^2-2*W*delta*cos(omega*tau)-4*alpha^2*beta*y
        +4*alpha^2*beta^2*y^2+4*alpha*beta*y^2+delta^2+x^2+W^2*tau^2*y^2*omega^2
        +W^2*tau^2*x^2*omega^2+2*W^2*tau^2*y*omega^2-2*W*x*delta*cos(omega*tau)
        -4*W*x*y*cos(omega*tau)-2*W*y*delta*cos(omega*tau)+2*W^2*tau^2*x*omega^2
        +4*W*tau*omega^2*cos(omega*tau)+2*W^2*x*y*cos(omega*tau)^2+2*W*x*alpha
        *cos(omega*tau)+2*W*y*alpha*cos(omega*tau)+4*alpha*beta*y*delta+4*alpha
        *beta*y*x+y^2+2*W^2*tau^2*x*y*omega^2+W^2*cos(omega*tau)^2+alpha^2)/omega^2:
>d_I := -(-4*alpha*omega+4*x*omega+4*y*omega+4*delta*omega-4*W*omega*cos(omega*tau)
          +8*alpha*beta*y*omega-4*W*x*omega*cos(omega*tau)
          -4*W*y*omega*cos(omega*tau))/omega^2:
>dd := simplify(d_I^2+d_R^2):
>xi := (W*(1+x+y)*cos(omega*tau)+alpha-2*alpha*beta*y-x-delta-y)/omega:
>chi_1 := -2-W*tau*(1+x+y)*cos(omega*tau):
>chi_2 := W*tau*(1+x+y)*sin(omega*tau):
>eta11 := 2*d_R+xi*d_I+d_R*chi_1-d_I*chi_2+I*(-chi_1*d_I-chi_2*d_R+d_R*xi-2*d_I):
>eta21 := 2*d_R+xi*d_I+d_R*chi_1+d_I*chi_2+I*(-chi_1*d_I+chi_2*d_R+d_R*xi-2*d_I):
>eta12 := eta11:
>eta22 := eta21:
>top := simplify(expand(E11*eta11+E12*eta12))/dd:
>z1 := p+I*q:
>z2 := p-I*q:
>realpart_top := coeff(top, I, 0):
>imagpart_top := coeff(top, I, 1):
>ppolyn_p := coeff(realpart_top, q, 0):
>ppolyn_q := coeff(imagpart_top, p, 0):
>Fp111 := coeff(coeff(realpart_top, q, 0), p^3):
>ppolyn_q := coeff(realpart_top, p, 0):
>Fp222 := coeff(ppolyn_q, q^3):
>Fp112 := coeff(coeff(realpart_top, p^2), q):
>Fp122 := coeff(coeff(realpart_top, p), q^2):
>Fq222 := coeff(ppolyn_q, q^3):
>Fq122 := coeff(coeff(imagpart_top, p), q^2):
>Fq112 := coeff(coeff(imagpart_top, p^2), q):
>Fq111 := coeff(coeff(imagpart_top, q, 0), p^3):
>m := 3.422*10^(-5):
>n := 1.101*10^(-7):
>theta := 3.422*10^(-11):
>W := (theta-m)/n:
>psi1 := 2*alpha*beta*y-alpha+x:
>psi2 := W*(1+y):
>psi3 := W*x*y:
```

```
>sin(omega*tau) := omega*(-omega^2*psi2-psi1^2*psi2+delta*psi3+psi1*psi3)
                          /(omega^2*psi2^2+(psi1*psi2-psi3)^2):
>cos(omega*tau) := (delta*omega^2*psi2+delta*psi1^2*psi2-delta*psi1*psi2
                    +omega^2*psi3)/(omega^2*psi2^2+(psi1*psi2-psi3)^2):
>a := 1/8*(3*Fp111+Fp122+Fq112+3*Fq222):
>alpha := 2.636:
>beta := 0.2e-2:
>delta := .3743:
>sigma := .1181:
>omega:= 2.25:
>phi := (alpha*beta*delta-W*alpha)^2+4*alpha*beta*W*sigma:
>x := (W*alpha-alpha*beta*delta-sqrt(phi))/(2*W):
>y := (alpha*(beta*delta+W)+sqrt(phi))/(2*W*alpha*beta):
>aa(omega, tau) -> a:
>with(plots): plot(aa(omega, tau), tau = 0.1e-5 .. 0.6e-2,
axes = boxed, font = [C, bold, 14],thickness = 4,
labels = [tau, "a"], labelfont = ["HELVETICA", 14],
color = "Blue", gridlines);
```

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