Analysis of Lauffenburger-Kennedy bacterial infection model for tissue inflammation dynamics

Yu Yang\textsuperscript{a}, Alhaji Cherif\textsuperscript{b} and Yuxin Zhang\textsuperscript{c}

\textsuperscript{a}College of Automation, Harbin Engineering University, Harbin, China; \textsuperscript{b}Wolfson Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford, United Kingdom; \textsuperscript{c}College of Science, Harbin Engineering University, Harbin, China

ABSTRACT

In this paper, we analyze a mathematical model for an inflammatory response to bacterial infection of homogeneous tissues. Specifically, we provide a detailed analysis of the Lauffenburger-Kennedy bacterial infection model and show that the model exhibits three possible equilibria corresponding to a bacteria-free and two endemic compromised steady states. Asymptotic results of the steady states along with the existences of saddle-node connection Hopf bifurcations are shown under certain conditions of the parameters. Within the biological ranges of the parameter values, we observe that the system can exhibit both forward and backward bifurcation. In addition, in both cases, the larger compromise bacterial infection steady state can either approach an equilibrium or can oscillate around it via Hopf bifurcation depending on the value of the ratio of leukocyte mortality to phagocytosis rates. Numerical results are used to provide illustrative examples of these different dynamical patterns observed in the model.

1. Introduction

In recent decades, mathematical models investigating dynamical patterns of inflammatory response to bacterial invasion of tissue have been considered \cite{2,4–8,14–16,18,23,25–27,29}. We consider the Lauffenburger-Kennedy model describing bacterial (\(B\)) and leukocyte (\(L\)) densities in a localized tissue region \cite{16}:

\[
\begin{align*}
\frac{dL}{dt} &= (h_0 + h_1 B) \frac{c_b A}{V} - \mu L, \\
\frac{dB}{dt} &= \frac{K_g K_i B}{K_i + B} - \frac{K_b B L}{K_b + B},
\end{align*}
\]

where \(h_0\) represents the normal emigration coefficient, \(h_1\) denotes the increase per unit local bacterial density-i.e. enhanced emigration coefficient, \(\mu\) is the mortality rate of leukocyte, and \(c_b\) is the localized leukocyte density circulating in the vasculature. The surface

CONTACT  Yuxin Zhang \textsuperscript{\textregistered} xyz.jl@163.com; Yu Yang \textsuperscript{\textregistered} yangyumath@163.com; Alhaji Cherif \textsuperscript{\textregistered} cherif@asu.edu

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
area of venule wall is denoted by $A$ and the tissue volume is represented by $V$. The bacterial growth rate is denoted by $K_g$, $K_i$ is the inhibition constant, $K_d$ is maximum per capita death rate of leukocyte, and the saturation rate is given by $K_b$. The first term of leukocyte density in Equation (1) represents the combined recruitment or emigration rate, and the second expression is the mortality rate of leukocyte. In this expression, the death rate is described as an exponential decay and emigration assumes a random process where production of both vasoactive substances (e.g. histamine) and chemical factors enhancing adherence of circulating leukocyte to blood vessel wall increase leukocyte emigration. In the bacteria population density equation, the first term denotes the growth rate, which increases exponentially for small bacterial density and saturates as density increases. The second term represents the bacterial death due to leukocyte phagocytosis (i.e. phagocytosis rate). Model (1) describes the tissue inflammation dynamics.

In this paper, we analytically investigate the following non-dimensionalized bacterial infection model for tissue inflammation dynamics:

$$\frac{du}{dt} = \rho(1 + \tau v - u), \quad t > 0,$$

$$\frac{dv}{dt} = \frac{\beta v}{1 + v} - \frac{uv}{k + v}, \quad t > 0,$$

where $u = L/L_0$ and $v = B/K_i$ are normalized leukocyte and bacterial density. Here $L_0 = h_0c_0A/\mu V$ and $\rho = \mu K_i/L_0K_d$ is the ratio of leukocyte death rate to maximum phagocytosis rate, $\tau = h_1K_i/h_0$ is a dimensionless ratio of enhanced phagocyte emigration rate to normal emigration rate and measures the sensitivity of leukocyte tissue infiltration rate during inflammation to the local bacterial density, $\beta = K_gK_i/K_dL_0$ is the ratio of maximum bacterial growth rate to maximum leukocyte phagocytosis rate, and $k = K_b/K_i$ represents the ratio of inhibitory effect of increasing bacteria density on bacterial growth to inhibitory effect of phagocytosis rate, respectively. Here $\tilde{t} = K_dL_0t/K_i$, where in Equation (2) we have dropped the “in $\tilde{t}$”. System (2) describes the inflammatory response to a bacterial invasion of tissue. Table 1 summarizes the parameters and state variables, where the parameter values were obtained from [16] and refs. therein. The dimensionless parameters are then calculated using the relationships between the parameters as outlined above. The values of these parameters play an important role in the analysis section and are used in the numerical simulation to illustrate different dynamics behaviours, where parameter values are selected within these ranges to show these different regimes.

There have been numerous works studying the above system to model bacterial infection. In particular, in [15,18], the authors used a simple mathematical model to describe the dynamical of local tissue inflammatory response to bacterial invasion, where spatially distributed conservation equations for tissue bacterial and leukocyte cell density were considered as a Metchnikoff-type predator-prey system [21]. Similarly, in [2], the authors developed a system of two coupled nonlinear ordinary differential equations, and use scaling arguments and singular perturbation techniques to study the dependency of the dynamic features of the inflammatory response on certain key parameters. Furthermore, Jing [11] showed the existence of bifurcation of saddle connection and the creation of limit cycles under certain conditions of the parameters. In [17], the author extended the model in [16] by incorporating diffusion and chemotaxis. Using a linear stability analysis, the author showed that when a phagocyte chemotactic response is smaller than a critical value...
Table 1. Dimensional and Dimensionless Parameters.

| Parameters | Description | Symbols | Values | Units | Refs. |
|------------|-------------|---------|--------|-------|-------|
| Normal emigration coefficient | $h_0$ | | $3 \times 10^{-6}$ | cm/hr | [1,10,16] |
| Enhanced emigration coefficient | $h_1$ | | $4 \times 10^{-14} - 4 \times 10^{-12}$ | cm/hr (bact/cm³) | [1,10,16] |
| Leukocyte mortality rate | $\mu$ | | $5 \times 10^{-2}$ | hr⁻¹ | [3,16] |
| Localized leukocyte density | $c_b$ | | $5 \times 10^6$ | leuk/cm³ | [13,16] |
| Venule surface area to tissue volume ratio | $A/V$ | | 300 | cm⁻¹ | [10,12,16,20] |
| Bacterial growth rate | $K_g$ | | 0.1 – 0.75 | hr⁻¹ | [10,16] |
| Inhibition constant | $K_i$ | | $10^7 - 10^9$ | bact/cm³ | [16] |
| Max. per capita death rate of leukocyte | $K_d$ | | 35 – 70 | bact/leuk hr | [16,19,24] |
| Saturation rate | $K_b$ | | $10^5 - 2.5 \times 10^7$ | bact/cm³ | [16,19,24] |
| Leukocyte death to phagocytosis rates ratio | $\rho$ | | 0.08 – 15.87 | – | calculated |
| Enhanced to normal emigration ratio | $\tau$ | | 0.13 – 1333 | – | calculated |
| Bacterial growth to leukocyte phagocytosis ratio | $\beta$ | | 0.16 – 238 | – | calculated |
| Ratio of inhibitory effects | $k$ | | $10^{-4} - 2.5$ | – | calculated |

the system can lead to a non-uniform state. However, if the chemotactic response is greater than this critical value, the system stabilizes to the uniform state. In [5], the author further extended the model constructed in [17] by incorporating bacterial taxis and provided similar steady states and stability analyses. In addition, the author discussed the possibility of having a non-uniform steady state, due to the combination of both chemotaxis and diffusion. Numerical simulations were used to check the effect of bacterial chemotaxis on the system's ability to exhibit Turing regimes. Assuming that the diffusion rate and the chemotactic rate are both very small compared to the growth rate, the authors in [22] derived a new equation to describe the time-evolution of the aggregating region and showed the conditions for the existence and stability of radially symmetric equilibrium solutions of the equation. Here, our focus is to revisit the model in Equation (2) to provide detailed analytic results underlying the observations in [16].

In the proceeding sections, we revisit the system described by Equation (2) with particular emphasis on complete and rigorous mathematical results of the stability of the steady states and on the bifurcation results and orbital stability of periodic solutions. In Section 2, we consider positivity and boundedness of the solutions and construct the feasible region where the model is biologically relevant. In Section 3, we establish the conditions for the existence of multiple endemic equilibria. In addition, the asymptotic stability conditions are provided for these equilibria in Section 4, and furthermore, bifurcation results and the existence of at least one limit cycles are provided. Section 5 provides illustrations of the various numerical simulations of the dynamic patterns predicted by our analytical results. Section 5 summarizes these results and provides a further research direction.

2. Positive invariant feasible region

The model (2) describes dynamics of bacterial infection for tissue inflammation, particularly the interaction between bacteria and phagocyte; and it is therefore critical to show that the model behaviours lie in a feasible region for which the model is biologically relevant. We need to show that the solutions to Equation (2) with natural initial non-negative conditions $(u(0), v(0)) = (u_0, v_0)$ will be confined in a biologically meaningful region (i.e.
the solution will remain non-negative) for all time $t \in \mathbb{R}^+$, where $\mathbb{R}^+ := [0, \infty)$. We have the following results:

**Theorem 2.1:** Solutions to system (2) with non-negative biologically relevant initial conditions $u(0) \geq 0$ and $v(0) \geq 0$ are non-negative for all time $t \in \mathbb{R}^+$. That is, solutions $u(t)$ and $v(t)$ remain in the set

$$
\Omega = \{(u, v) \in \mathbb{R}^2_+ : u \geq 0, v \geq 0\}.
$$

Furthermore, the following holds:

1. If $v(0) = 0$, then all solutions $v(t)$ remain zero;
2. If $v(0) > 0$, then all solutions remain inside the feasible region $\Omega$.

**Proof:** Let $u(0) \geq 0$ and $v(0) \geq 0$ be the initial conditions of $u(t)$ and $v(t)$, respectively. Clearly, if $v(0) = 0$, then $v(t) = 0$ for all $t \geq 0$. In the case $v(0) > 0$, suppose there exist $T_0 := \inf \{t \in \mathbb{R}^+ : v(t) = 0\}$ such that $v(t) > 0$ for all $0 < t < T_0$ and $v(T_0) = 0$. That is, $T_0$ is the first time when $v(t) = 0$. Now let,

$$
A = \min_{0 \leq t \leq T_0} \left\{ \frac{\beta v}{1 + v} - \frac{u}{k + v} \right\},
$$

then for all $t \in [0, T_0]$, the expression for $v(t)$ becomes

$$
\frac{dv}{dt} = \frac{\beta v}{1 + v} - \frac{uv}{k + v} \geq A v.
$$

Therefore, $v(t) \geq v(0) e^{At}$. Then evaluating $v(t)$ at time $t = T_0$, we observe that $v(T_0) \geq v(0) e^{A T_0} > 0$, which is a contradiction. This implies $v(t) > 0$ for all time $t \in \mathbb{R}^+$.

Similarly, since $v(t) \geq 0$ for all $t \in \mathbb{R}^+$, we observe that,

$$
\frac{du}{dt} = \rho (1 + \tau v - u) \geq \rho (1 - u).
$$

Hence $u(t) \geq 1 + (u(0) - 1) e^{-\rho t} \geq 1$ provided that $u(0) \geq 1$. If $u(0) < 1$, we have $u(t) \geq 1 - (1 - u(0)) e^{-\rho t} \geq 0$. Therefore, $u(t)$ and $v(t)$ are non-negative for all $t \in \mathbb{R}^+$. That is, $u(t)$ and $v(t)$ remain in the region

$$
\Omega = \{(u, v) \in \mathbb{R}^2_+ : u \geq 0, v \geq 0\}.
$$

This completes the proof. $\blacksquare$

### 3. Steady states analysis

In this section, we consider the steady state solutions of the model described by Equation (2) augmented with the following initial conditions:

$$
u(0) = u_0 \geq 0, \quad v(0) = v_0 \geq 0.
$$

We observe that the system given by Equation (2) with the above initial data admits a semi-trivial equilibrium given by $E_0 = (u, v) = (1, 0)$; and we call this steady state the infection-free (elimination) equilibrium, where bacteria is absent or eradicated from the tissue.
should be noted that the infection-free equilibrium exists. In addition, we observe that Equation (2) can also allow non-trivial steady states or endemic (compromise) equilibria, depending on the model parameters. Following [5, 16] and solving

\[ 1 + \tau v - u = 0, \quad \frac{\beta (1 + v)(1 + \tau v)}{k + v} = \beta, \tag{10} \]

we can obtain a quadratic expression, which has two solutions where the system (2) has a positive steady state \((u, v)\) if and only if

\[ h(v) := \frac{(1 + v)(1 + \tau v)}{k + v} = \beta, \tag{11} \]

and \(u = 1 + \tau v > 0\). Clearly, we can directly calculate the exact expression using quadratic formula. However, because our aim herein is to obtain the necessary conditions for the various dynamical patterns, we instead use Equation (10) to obtain the necessary conditions for the existence of endemic equilibria in order to simplify the calculations. In particular, we observe that \(h(v)\) has the following properties:

1. If \(k \geq 1/(1 + \tau)\) holds, then \(h(v)\) is increasing for all \(v > 0\);
2. If \(0 < k < 1/(1 + \tau)\) holds, then \(h(v)\) is decreasing for all \(v \in (0, \lambda_0)\) and increasing for all \(v > \lambda_0\), where

\[ \lambda_0 := \sqrt{k^2 - (k + k\tau - 1)/\tau} - k > 0, \]

and \(h(v)\) attains its minimal positive value \(h(\lambda_0)\) at \(v = \lambda_0\).

Noting that \(h(0) = 1/k\) and from the aforementioned properties of \(h(v)\), we state the following results on the existence of a positive equilibrium of the system (2).

**Lemma 3.1:** Let \(h(v)\) be defined in (10) and \(\lambda_0\) be defined by (11), then the following conclusions hold:

1. Suppose that \(k \geq 1/(1 + \tau)\) holds, that is, \(h(v)\) is increasing for all \(v > 0\). Then,
   (a) If \(\beta \leq 1/k\) holds, then system (2) has no positive equilibrium solution;
   (b) If \(\beta > h(0) = 1/k\) holds, then system (2) has a unique positive solution \((u_\lambda, \lambda)\), where \(\lambda > 0\) solves \(\beta = h(v)\) and \(u_\lambda = 1 + \tau \lambda\).

2. Suppose that \(0 < k < 1/(1 + \tau)\) holds. Then,
   (a) If \(\beta < h(\lambda_0)\) holds, then system (2) has no positive equilibrium solutions;
   (b) If \(\beta = h(\lambda_0)\) holds, then system (2) has a unique positive solution \((u_{\lambda_0}, \lambda_0)\);
   (c) If \(h(\lambda_0) < \beta < 1/k\) holds, then system (2) has exactly two different positive equilibrium solutions, denoted by \((u_\mu, \mu)\) and \((u_\lambda, \lambda)\), with \(0 < \mu < \lambda_0 < \lambda\) such that \(h(\mu) = h(\lambda) = \beta\), and \(u_\mu = 1 + \tau \mu, u_\lambda = 1 + \tau \lambda\);
   (d) If \(\beta \geq 1/k\) holds, then system (2) has a unique positive equilibrium solution \((u_\lambda, \lambda)\) with \(\lambda \geq \lambda_* > \lambda_0\), where \(\lambda_*\) satisfies \(h(\lambda_*) = 1/k\), and \(u_\lambda = 1 + \tau \lambda\).

The proof of Lemma 3.1 is trivial and will be omitted herein. From Lemma 3.1, the steady states are determined by only \(k, \beta\) and \(\tau\). In addition, we observe that the system (2)
can undergo both forward (see Lemma 3.1(1)) and backward (see Lemma 3.1(2)) steady state bifurcations. In the proceeding discussion, we will consider and establish the necessary conditions for the stability of these equilibria. Throughout this paper, we denote the infection-free and the two endemic equilibria by $E_0, E_\lambda$, and $E_\mu$, respectively.

4. Stability and bifurcation analysis

We now consider the local stability of the infection-free $E_0 = (1, 0)$, the positive equilibrium solutions $E_\mu = (u_\mu, \mu)$ and $E_\lambda = (u_\lambda, \lambda)$ provided that they exist, where $\mu < \lambda$.

4.1. Infection-free equilibrium, $E_0$

Examining the characters of the eigenvalues of the Jacobian matrix obtained from the linearization of Equation (2) at the infection-free equilibrium, we state the following conclusions:

**Theorem 4.1:** The infection-free equilibrium $E_0 = (1, 0)$ is stable if $R_0 = \beta k < 1$, and unstable if $R_0 = \beta k > 1$. However, if $R_0 = \beta k = 1$, then $E_0$ is stable if $k \geq 1$, and unstable if $0 < k < 1$.

**Proof:** The linearized operator evaluated at $(1, 0)$ is given by

$$L(\lambda) := \begin{pmatrix} -\rho & \rho \tau \\ 0 & -\frac{1}{k} + \beta \end{pmatrix}.$$ (12)

Therefore, the eigenvalues are given by $-\rho$ and $-1/k + \beta$. Hence, if $R_0 = \beta k < 1$, then the infection-free equilibrium $E_0$ is locally asymptotically stable; and it is otherwise unstable if $R_0 = \beta k > 1$. In addition, at $R_0 = \beta k = 1$, the eigenvalues of system (2) linearized at the infection-free equilibrium are $-\rho$ and 0.

To establish results under the condition of $R_0 = \beta k = 1$, we use the center manifold methods ([9]), and reformulate the problem using the abstract setting. In particular, we first translate the infection-free equilibrium $E_0$ to the origin, where $\tilde{u} = u - 1$, $\tilde{v} = v$. For convenience, we drop the $\tilde{\cdot}$ in $\tilde{u}$ and $\tilde{v}$, and use $u$ and $v$, respectively. Hence, the local system (2) becomes

$$\frac{dv(t)}{dt} = \frac{\beta v}{1 + v} - \frac{v(1 + u)}{k + v},$$

$$\frac{du(t)}{dt} = -\rho u + \rho \tau v.$$ (13)

From the center manifolds theory of [9], there exists a center manifold for system (13) which can locally be represented as follows

$$W^c(0) = \{(v, u) \in \mathbb{R}^2 \mid u = h(v), \ |v| < \delta, \ h(0) = Dh(0) = 0\}$$ (14)

for $\delta > 0$ sufficiently small. To compute $W^c(0)$, we assume that $h(v)$ has the form

$$h(v) = av^2 + bv^3 + o(v^4).$$ (15)
Then, the equation for the center manifold is given by
\[
Dh(v) \left( \frac{\beta v}{1 + v} - \frac{v(1 + h(v))}{k + v} \right) + \rho h(v) - \rho \tau v = 0, \tag{16}
\]
which can be rewritten as follows,
\[
(2av + 3bv^2 + \cdots) \left( \frac{\beta v}{1 + v} - \frac{v(1 + av^2 + bv^3 + \cdots)}{k + v} \right) + \rho (av^2 + bv^3 + \cdots) - \rho \tau v = 0. \tag{17}
\]
Hence,
\[
\beta v (2av + 3bv^2 + \cdots) (k + v) - v (2av + 3bv^2 + \cdots) (1 + av^2 + bv^3 + \cdots) (1 + v) + \rho (av^2 + bv^3 + \cdots) (1 + v) (k + v) - \rho \tau v (1 + v) (k + v) = 0. \tag{18}
\]
Because the coefficient of \( v \) in the left-hand side of Equation (18) is \(-\rho \tau k \neq 0\), we have \( v \equiv 0 \). Hence, \( h(v) \equiv 0 \). Then the system (2) restricted to the center manifold is, for \( v \) sufficiently small, given by the following expression
\[
\frac{dv(t)}{dt} = \frac{\beta v}{1 + v} - \frac{v}{k + v}. \tag{19}
\]
It is easy to check that when \( k \geq 1 \), then the zero solution of (19) is stable on one hand. If \( 0 < k < 1 \), then the zero solution of (19) is unstable on the other hand. Therefore, from the center manifold theorem of [9], it follows that if \( 1/\beta = k \geq 1 \), then \( E_0 \) is stable in the original system (2), while unstable when \( 1/\beta = k \in (0,1) \). This completes the proof. ■

It follows from Lemma 3.1 and Theorem 4.1 immediately that the following result holds.

**Corollary 4.2:** If 1(a) of Lemma 3.1 holds: \( 0 < k < 1 \), then \( E_0 \) is unstable; \( k \geq 1 \), then \( E_0 \) is stable. If 2(a) of Lemma 3.1 holds, then \( E_0 \) is stable.

### 4.2. Endemic equilibria, \( E_\mu \) and \( E_\lambda \)

In the previous section, we establish that, when \( R_0 < 1 \), the infection-free equilibrium is locally asymptotically stable. Moreover, when \( R_0 > 1 \), the infection-free equilibrium is unstable, and there is at least one non-trivial solution. In this section, we consider the stability of endemic equilibria.

**Theorem 4.3:** The following statements hold:

1. Suppose that part 1(b) of Lemma 3.1 holds. Then, \( E_\lambda = (u_\lambda, \lambda) \) is stable for all \( \lambda > 0 \) if \( k \geq 1 \) or \( 1/(1 + \tau) < k < 1 \) but \( \rho > A(\lambda_{**}) \), or for any \( \lambda \in (0, \lambda_1) \cup (\lambda_2, \infty) \) if \( 1/(1 + \tau) < k < 1 \) but \( 0 < \rho < A(\lambda_{**}) \), where
\[
A(\lambda) := \frac{\lambda(1 + \tau \lambda)(1 - k)}{(1 + \lambda)(k + \lambda)^2}, \tag{20}
\]
and \( \lambda_{**} \) is the unique maximum point of \( A(\lambda) \), and \( \lambda_1, \lambda_2 \) are the two roots of \( A(\lambda) = \rho \) with \( \lambda_1 < \lambda_2 \). In addition, the endemic equilibrium \( E_\lambda = (u_\lambda, \lambda) \) is unstable for any
\[ \lambda \in (\lambda_1, \lambda_2) \text{ if } 1/(1 + \tau) < k < 1 \text{ and } 0 < \rho < A(\lambda_{**}). \text{ Moreover, at } \lambda = \lambda_1 \text{ and } \lambda_2, \text{ the system given by Equation (2) undergoes Hopf bifurcations;} \]

(2) Suppose that \( \lambda_0 \) is defined precisely in Equation (11) and part 2(b) of Lemma 3.1 holds. Then, the unique positive equilibrium solution \( E_\lambda = (u_{\lambda_0}, \lambda_0) \) is always unstable;

(3) Suppose that part 2(c) of Lemma 3.1 holds. Then, the 'smaller' positive equilibrium solution \( E_\lambda = (u_{\mu}, \lambda) \) is always unstable; and the 'lager' positive equilibrium solution \( E_\lambda = (u_{\lambda}, \lambda) \) is stable for any \( \lambda \) if \( \rho > A(\lambda_{**}) \), or \( 0 < \rho < A(\lambda_{**}) \) but \( \lambda \in \Lambda \), and otherwise unstable if \( 0 < \rho < A(\lambda_{**}) \) but \( \lambda \in \Lambda^* \), where

\[
\Lambda := \begin{cases} 
(\lambda_0, \lambda_1) \cup (\lambda_2, \infty), & \text{if } \lambda_1 > \lambda_0; \\
(\lambda_2, \infty), & \text{if } \lambda_2 > \lambda_0 > \lambda_1; \\
(\lambda_0, \infty), & \text{if } \lambda_0 > \lambda_2; \\
(\lambda_0, \lambda_2), & \text{if } \lambda_1 > \lambda_0, \\
(\lambda_1, \lambda_2), & \text{if } \lambda_2 > \lambda_0 > \lambda_1. 
\end{cases} \\
\Lambda^* := \begin{cases} 
(\lambda_0, \lambda_1) \cup (\lambda_2, \infty), & \text{if } \lambda_1 > \lambda_*; \\
(\lambda_2, \infty), & \text{if } \lambda_2 > \lambda_* > \lambda_1; \\
(\lambda_*, \infty), & \text{if } \lambda_* > \lambda_2; \\
(\lambda_*, \lambda_2), & \text{if } \lambda_1 > \lambda_*; \\
(\lambda_1, \lambda_2), & \text{if } \lambda_2 > \lambda_* > \lambda_1. 
\end{cases}
\]

\[(21)\]

In addition, when \( \rho > A(\lambda_{**}) \), the system (2) does not undergo Hopf bifurcations. When \( 0 < \rho < A(\lambda_{**}) \): if \( \lambda_0 < \lambda_1 \), then at \( \lambda = \lambda_1 \) and \( \lambda_2 \), the system (2) undergoes Hopf bifurcations; if \( \lambda_1 < \lambda_0 < \lambda_2 \), then the system (2) undergoes Hopf bifurcations only at \( \lambda = \lambda_2 \); while if \( \lambda_0 > \lambda_2 \), then system (2) does not undergo Hopf bifurcations.

(4) Suppose that part 2(d) of Lemma 3.1 holds. Then, \( E_\lambda = (u_{\lambda_1}, \lambda) \) is stable for all \( \lambda \) if \( \rho > A(\lambda_{**}) \), or \( 0 < \rho < A(\lambda_{**}) \) but \( \lambda \in \Lambda \), and otherwise unstable if \( 0 < \rho < A(\lambda_{**}) \) but \( \lambda \in \Lambda^* \), where

\[
\Lambda := \begin{cases} 
(\lambda_*, \lambda_1) \cup (\lambda_2, \infty), & \text{if } \lambda_1 > \lambda_*; \\
(\lambda_2, \infty), & \text{if } \lambda_2 > \lambda_* > \lambda_1; \\
(\lambda_*, \infty), & \text{if } \lambda_* > \lambda_2; \\
(\lambda_*, \lambda_2), & \text{if } \lambda_1 > \lambda_*; \\
(\lambda_1, \lambda_2), & \text{if } \lambda_2 > \lambda_* > \lambda_1. 
\end{cases} \\
\Lambda^* := \begin{cases} 
(\lambda_0, \lambda_1) \cup (\lambda_2, \infty), & \text{if } \lambda_1 > \lambda_*; \\
(\lambda_2, \infty), & \text{if } \lambda_2 > \lambda_* > \lambda_1; \\
(\lambda_*, \infty), & \text{if } \lambda_* > \lambda_2; \\
(\lambda_*, \lambda_2), & \text{if } \lambda_1 > \lambda_*; \\
(\lambda_1, \lambda_2), & \text{if } \lambda_2 > \lambda_* > \lambda_1. 
\end{cases}
\]

\[(22)\]

Furthermore, when \( \rho > A(\lambda_{**}) \), the system (2) does not undergo Hopf bifurcations. When \( 0 < \rho < A(\lambda_{**}) \): if \( \lambda_* < \lambda_1 \), then at \( \lambda = \lambda_1, \lambda_2 \), the system (2) undergoes Hopf bifurcations. Moreover, if \( \lambda_1 < \lambda_* < \lambda_2 \), then the system (2) undergoes Hopf bifurcations only at \( \lambda = \lambda_2 \), and for \( \lambda_* > \lambda_2 \), the system (2) does not undergo Hopf bifurcations.

**Proof:** 1. Suppose that part 1(b) of Lemma 3.1 holds. Then, the linearized operator evaluated at \( E_\lambda = (u_{\lambda_1}, \lambda) \) is given by

\[
L(\lambda) := \begin{pmatrix} -\rho & \rho \tau \\ -\frac{\lambda}{k + \lambda} & \frac{\lambda (1 + \tau \lambda)(1 - k)}{(1 + \lambda)(k + \lambda)^2} \end{pmatrix}
\]

with the following characteristic equation \( P_\lambda(\sigma) = \sigma^2 - T(\lambda)\sigma + D(\lambda) = 0 \), where

\[
T(\lambda) = \frac{\lambda (1 + \tau \lambda)(1 - k)}{(1 + \lambda)(k + \lambda)^2} - \rho = A(\lambda) - \rho, \quad D(\lambda) = \frac{\rho \lambda}{1 + \lambda} h'(\lambda).
\]

\[(24)\]

Because \( h'(\lambda) > 0 \), then we have \( D(\lambda) > 0 \). If \( k \geq 1 \), then for all \( \lambda > 0 \), we observe that \( T(\lambda) < 0 \). In this case, \( E_\lambda = (u_{\lambda_1}, \lambda) \) is stable.
We now consider the case when $1/(1 + \tau) < k < 1$. We can easily check that,

$$A'(\lambda) = \frac{(1 - k)G(\lambda)}{(1 + \lambda)^2(k + \lambda)^3},$$

where

$$G(\lambda) := -\tau \lambda^3 + (k - 2)\lambda^2 + (2\tau - 1)\lambda + k.$$  \hfill (25)

Then, there exists a unique $\tilde{\lambda} > 0$, such that $G(\lambda) > 0$ for any $\lambda < (0, \tilde{\lambda})$ and $G(\lambda) < 0$ for any $\lambda \in (\tilde{\lambda}, \infty)$. If $k > 0$, we observe that $G'(\lambda) = -3\tau \lambda^2 + 2(k - 2)\lambda + 2\tau - 1, G'(0) = 2\tau - 1$. Therefore, if $2k\tau - 1 > 0$, then $G'(\lambda) > 0$ for two real roots of opposite signs. If $2k\tau - 1 \leq 0$, then $k\tau - 2 < 0$ and it is easy to show that $G'(\lambda) = 0$ has two distinct nonpositive real roots. Obviously, we note that $G(0) = k > 0$. Hence, for any $k$ and $\tau$, $\tilde{\lambda}$ must exist and be unique. Thus, there also exists a $\lambda_{**} > 0$ such that $A(\lambda)$ is increasing in $(0, \lambda_{**})$, and decreasing in $(\lambda_{**}, \infty)$. In addition, $A(\lambda)$ attains its maximal positive value at $\lambda = \lambda_{**}$.

If $\rho > A(\lambda_{**})$, then we have $T(\lambda) < 0$ for any $\lambda > 0$. Hence, the endemic equilibrium $E_\lambda = (u_\lambda, \lambda)$ is locally asymptotically stable. If $0 < \rho < A(\lambda_{**})$, then there exists two points $\lambda_1$ and $\lambda_2$ such that $A(\lambda_1) = A(\lambda_2) = \rho$ with $\lambda_1 < \lambda_2$. For any $\lambda \in (0, \lambda_1) \cup (\lambda_2, \infty)$, we have $T(\lambda) < 0$, and for any $\lambda \in (\lambda_1, \lambda_2)$, we have $T(\lambda) > 0$. Thus, if $0 < \rho < A(\lambda_{**})$ and $\lambda \in (0, \lambda_1) \cup (\lambda_2, \infty)$, $E_\lambda = (u_\lambda, \lambda)$ is stable; and it is otherwise unstable if $0 < \rho < A(\lambda_{**})$ and $\lambda \in (\lambda_1, \lambda_2)$.

Now suppose $0 < \rho < A(\lambda_{**})$ and $\lambda = \lambda_1$ or $\lambda = \lambda_2$, then $\rho = A(\lambda)$ and $T(\lambda) = 0$. Let

$$\rho_0 := \frac{\lambda(1 + \tau\lambda)(1 - k)}{(1 + \lambda)(k + \lambda)^2}.$$ \hfill (27)

Then when $\rho = \rho_0$, the Jacobian matrix $L(\lambda)$ has a pair of imaginary eigenvalues $\sigma = \pm i\sqrt{h'(\lambda)}\rho_0\lambda/(1 + \lambda)$. Let $i\sigma = \psi(\rho) = \pm i\phi(\rho)$ be the roots of the characteristic polynomial $P_\lambda(\sigma) = \sigma^2 - \sigma T + D = 0$. Then

$$\psi(\rho) = \frac{\lambda(1 + \tau\lambda)(1 - k)}{2(1 + \lambda)(k + \lambda)^2} - \frac{1}{2}\rho,$$ \hfill (28)

and $\psi'(\rho)|_{\rho=\rho_0} = -\frac{1}{2} < 0$ which is nonzero. Thus, the system (2) undergoes Hopf bifurcations at $(u_\lambda, \lambda)$.

2. Suppose that part 2(b) of Lemma 3.1 holds. The system (2) has a unique positive solution $E_\lambda = (u_{\lambda_0}, \lambda_0)$; and the characteristic equation of system (2) at $E_\lambda = (u_{\lambda_0}, \lambda_0)$ is $P_\lambda(\sigma) = \sigma^2 - T(\lambda_0)\sigma + D(\lambda_0) = 0$, where

$$T(\lambda_0) = A(\lambda_0) - \rho, \quad D(\lambda_0) = \frac{\rho\lambda_0}{1 + \lambda_0}h'(\lambda_0).$$ \hfill (29)

Since 2(b) of Lemma 3.1 holds, then $\beta = h(\lambda_0)$ and $h'(\lambda_0) = 0$. Hence, $D(\lambda_0) = 0$. In addition, the eigenvalues of the system (2) linearized at $E_\lambda = (u_{\lambda_0}, \lambda_0)$ are $A(\lambda_0) - \rho$ and 0. If $\rho < A(\lambda_0)$, then $(u_{\lambda_0}, \lambda_0)$ is unstable because the eigenvalue $A(\lambda_0) - \rho > 0$.

We now consider $\rho \geq A(\lambda_0)$, and translate the equilibrium $(u_{\lambda_0}, \lambda_0)$ to the origin with $\tilde{u} = u - (1 + \tau\lambda_0), \tilde{v} = v - \lambda_0$. For the sake of convenience, we drop the \(\tilde{\text{in}}\) $\tilde{u}$ and $\tilde{v}$, and
Therefore, the equation for the center manifold is given by
\[
\frac{du(t)}{dt} = (A(\lambda_0) - \rho)u + \rho \tau v - A(\lambda_0)u. \tag{30}
\]

By the center manifold theorem of [9], there exists a center manifold for the system (30) which can locally be represented as follows,
\[
\tilde{W}^c(0) = \{ (v, u) \in \mathbb{R}^2 \mid u = \tilde{h}(v), \ |v| < \delta, \ \tilde{h}(0) = D\tilde{h}(0) = 0 \} \tag{31}
\]
for \( \delta > 0 \) sufficiently small. To compute \( \tilde{W}^c(0) \), we assume that \( \tilde{h}(v) \) has the following form,
\[
\tilde{h}(v) = \tilde{a}v^2 + \tilde{b}v^3 + o(v^4). \tag{32}
\]

Therefore, the equation for the center manifold is given by
\[
D\tilde{h}(v) \left( \frac{\beta(v + \lambda_0)}{1 + v + \lambda_0} - \frac{(v + \lambda_0)(1 + \tau \lambda_0 + \tilde{h}(v))}{k + v + \lambda_0} \right) - (A(\lambda_0) - \rho)\tilde{h}(v) - (\rho \tau v - A(\lambda_0)u) = 0, \tag{33}
\]
which can be equivalently rewritten as
\[
(2\tilde{a}v + 3\tilde{b}v^2 + \cdots) \left( \frac{\beta(v + \lambda_0)}{1 + v + \lambda_0} - \frac{(v + \lambda_0)(1 + \tau \lambda_0 + \tilde{a}v^2 + \tilde{b}v^3 + \cdots)}{k + v + \lambda_0} \right) + \rho(\tilde{a}v^2 + \tilde{b}v^3 + \cdots) - \rho \tau v = 0. \tag{34}
\]

Rewriting the express above, we have
\[
\beta(\lambda_0 + v)(2\tilde{a}v + 3\tilde{b}v^2 + \cdots)(k + \lambda_0 + v) - (\lambda_0 + v)(2\tilde{a}v + 3\tilde{b}v^2 + \cdots) \\
\times (1 + \tau \lambda_0 + \tilde{a}v^2 + \tilde{b}v^3 + \cdots)(1 + \lambda_0 + v) + \rho(\tilde{a}v^2 + \tilde{b}v^3 + \cdots) \\
\times (1 + \lambda_0 + v)(k + \lambda_0 + v) - \rho \tau v(1 + \lambda_0 + v)(k + \lambda_0 + v) = 0. \tag{35}
\]

Because the coefficient of \( v \) in the left of (35) is
\[
\beta \lambda_0(1 + \lambda_0)(2\tilde{a} - \lambda_0)(1 + \tau \lambda_0)(1 + \lambda_0)2\tilde{a} - \rho \tau (1 + \lambda_0)(k + \lambda_0) \\
= -\rho \tau (1 + \lambda_0)(k + \lambda_0) \neq 0, \tag{36}
\]
we conclude that \( v \equiv 0 \). Therefore, \( \tilde{h}(v) \equiv 0 \). Then the system (2) restricted to the center manifold is, for \( v \) sufficiently small, given by the following system
\[
\frac{dv(t)}{dt} = \frac{v(1 - k)(1 + \tau \lambda_0)(v + \lambda_0)}{(k + \lambda_0)(1 + v + \lambda_0)(k + v + \lambda_0)}. \tag{37}
\]

Under part 2(b), we have \( 0 < k < 1/(1 + \tau) \). Hence, the zero solution of Equation (37) is unstable, which implies that \( \mathcal{E}_\lambda = (u_{\lambda_0}, \lambda_0) \) is unstable in the original system (2).
3. Suppose that part 2(c) of Lemma 3.1 holds. Then both \( \mathcal{E}_\mu = (u_\mu, \mu) \) and \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) exist. The linearized operator of system (2) evaluated at \( \mathcal{E}_\mu = (u_\mu, \mu) \) is given by

\[
L(\mu) := \begin{pmatrix}
-\frac{\rho}{\mu} & \frac{\rho \tau}{(1 + \mu)(k + \mu)^2} \\
-\frac{\mu}{k + \mu} & \mu(1 + \tau \mu)(1 - k)
\end{pmatrix}
\]

with the following characteristic equation \( P_\mu(\sigma) = \sigma^2 - T(\mu)\sigma + D(\mu) = 0 \), where

\[
T(\mu) = \frac{\mu(1 + \tau \mu)(1 - k)}{(1 + \mu)(k + \mu)^2} - \rho, \quad D(\mu) = \frac{\rho \mu}{1 + \mu} h'(\mu).
\]

By the definition of \( \mathcal{E}_\mu = (u_\mu, \mu) \), it follows that \( h'(\mu) < 0 \), which implies that \( \mathcal{E}_\mu = (u_\mu, \mu) \) is unstable whenever it exists.

We now consider the stability of the endemic equilibrium \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \). If \( \rho > A(\lambda_{**}) \) holds, then for any \( \lambda \) we have \( T(\lambda) < 0 \). Hence, the system (2) does not undergo Hopf bifurcations, and the endemic equilibrium \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable. In addition, if \( 0 < k < 1/(1 + \tau), 0 < \rho < A(\lambda_{**}) \) and \( \lambda_1 > \lambda_0 \), then \( T(\lambda) < 0 \) for any \( \lambda \in (\lambda_0, \lambda_1) \) and \( \lambda > \lambda_0 \). Hence, \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable. For any \( \lambda \in (\lambda_1, \lambda_2) \), we have \( T(\lambda) > 0 \) which implies that \( \mathcal{E}_\lambda \) is unstable. Moreover, if \( 0 < k < 1/(1 + \tau) \), \( 0 < \rho < A(\lambda_{**}) \) and \( \lambda_2 > \lambda_0 > \lambda_1 \), then \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable for any \( \lambda \in (\lambda_2, \infty) \). Otherwise, if \( \lambda \in (\lambda_0, \lambda_2) \), then \( T(\lambda) > 0 \). Hence, \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is unstable. Furthermore, if \( 0 < k < 1/(1 + \tau) \), \( 0 < \rho < A(\lambda_{**}) \) and \( \lambda_0 > \lambda_2 \), then \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable for any \( \lambda \in (\lambda_0, \infty) \).

If \( 0 < \rho < A(\lambda_{**}) \) but \( \lambda_0 < 1/\lambda_2 \), there exists \( \rho_0 = A(\lambda_1), A(\lambda_2) \). Then \( T(\lambda) = 0 \) for \( \lambda = \lambda_1, \lambda_2 \) and \( \psi'(\rho)|_{\rho=\rho_0} = -1/2 < 0 \) which is nonzero. Hence, \( \lambda_1 \) and \( \lambda_2 \) are Hopf bifurcation points. We observe that when \( \lambda_1 < \lambda_0 < \lambda_2 \) holds, then \( \lambda_2 \) is the only Hopf bifurcation point; and when \( \lambda_0 > \lambda_2 \), the system does not have Hopf bifurcation point.

4. Suppose that part 2(d) of Lemma 3.1 holds, then \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) exists. If \( \rho > A(\lambda_{**}) \), then \( T(\lambda) < 0 \) for any \( \lambda \). Hence, the endemic equilibrium \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable, and the system (2) does not undergo Hopf bifurcations.

If \( 0 < \rho < A(\lambda_{**}) \) and \( \lambda > \lambda_{**} > \lambda_0 \) holds. Now we consider the stability of the equilibrium solution \( (u_\lambda, \lambda) \). Similarly, we know that if \( 0 < k < 1/(1 + \tau) \) and \( \lambda_1 > \lambda_0 \), then \( T(\lambda) < 0 \) for any \( \lambda \in (\lambda_{**}, \lambda_1) \cup (\lambda_2, \infty) \). Hence, the endemic \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable. For any \( \lambda \in (\lambda_1, \lambda_2) \), we have \( T(\lambda) > 0 \) which implies that \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is unstable. If \( 0 < k < 1/(1 + \tau) \) and \( \lambda_2 > \lambda_{**} > \lambda_1 \), then \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable for any \( \lambda \in (\lambda_2, \infty) \) and \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is unstable for any \( \lambda \in (\lambda_{**}, \lambda_2) \). Moreover, if \( 0 < k < 1/(1 + \tau) \) and \( \lambda_{**} > \lambda_2 \), then for any \( \lambda \in (\lambda_{**}, \infty) \) and \( T(\lambda) < 0 \), \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is locally asymptotically stable. Furthermore, if \( 0 < \rho < A(\lambda_{**}) \) but \( \lambda_{**} < \lambda_1 < \lambda_2 \), there also exists \( \rho_0 = A(\lambda_1), A(\lambda_2) \). Then \( T(\lambda) = 0 \) for \( \lambda = \lambda_1, \lambda_2 \) and \( \psi'(\rho)|_{\rho=\rho_0} \) is nonzero. Hence, \( \lambda_1 \) and \( \lambda_2 \) are Hopf bifurcation points. When \( \lambda_1 < \lambda_{**} < \lambda_2 \) holds, then \( \lambda_2 \) is the only Hopf bifurcation point; and when \( \lambda_{**} > \lambda_2 \), the system does not have Hopf bifurcation point. This completes the proof.

**Theorem 4.4:** Suppose that either part 2(c) or part 2(d) of Lemma 3.1 hold. Then the periodic solution bifurcating from \( \mathcal{E}_\lambda = (u_\lambda, \lambda) \) is orbitally stable if \( a > a_0 \), and it is unstable when \( a < a_0 \), where \( a_0 \) is defined in Equation (62).
**Proof:** To study the existence of Hopf bifurcation occurring at the unique equilibrium point \( E_{\tilde{\lambda}} = (u^*, v^*) = (u_\lambda, \lambda) = (1 + \tau \lambda, \lambda) \), we choose \( \lambda \) as the bifurcation parameter, and let \( \bar{\lambda} \) be defined as

\[
\tilde{\lambda}(1 + \tau \bar{\lambda})(1 - k) = \rho. \tag{40}
\]

Then when \( \lambda = \bar{\lambda} \), the Jacobian matrix \( L(\lambda) \) has a pair of imaginary eigenvalues \( \sigma = \pm i \sqrt{h'(\bar{\lambda}) \rho \bar{\lambda}/(1 + \bar{\lambda})} \). Let \( \sigma = \psi(\lambda) \pm i \omega(\lambda) \) be the roots of the characteristic polynomial \( P_\lambda(\sigma) = \sigma^2 - \sigma T + D = 0 \). Then,

\[
\psi(\lambda) = \frac{\lambda(1 + \tau \lambda)(1 - k)}{2(1 + \lambda)(k + \lambda)^2} - \frac{1}{2} \rho, \tag{41}
\]

and

\[
\omega(\lambda) = \frac{1}{2} \sqrt{\frac{4 h'(\lambda) \rho \lambda}{1 + \lambda} - \left( \frac{\lambda(1 + \tau \lambda)(1 - k)}{(1 + \lambda)(k + \lambda)^2} - \rho \right)^2}. \tag{42}
\]

By the application of Poincaré-Andronov-Hopf bifurcation theorem [9], we note that the system (2) undergoes a Hopf bifurcation at \( E_{\tilde{\lambda}} \) when \( \lambda = \bar{\lambda} \). However, the detailed nature of the Hopf bifurcation needs further analysis of the normal form of the system. To that end, we translate the equilibrium \( E_{\tilde{\lambda}} = (u^*, v^*) \) to the origin. Let \( \tilde{u} = u - u^*, \tilde{v} = v - v^* \). For the sake of convenience, we drop \( \tilde{\lambda} \) in \( \tilde{u} \) and \( \tilde{v} \) and use \( u \) and \( v \), respectively. After some calculations, the local system (2) becomes

\[
\begin{align*}
\frac{du(t)}{dt} &= \rho(\tau v - u), \\
\frac{dv(t)}{dt} &= \frac{\beta(v + \lambda)}{1 + v + \lambda} - \frac{(u + 1 + \tau \lambda)(v + \lambda)}{k + v + \lambda}.
\end{align*} \tag{43}
\]

Rewriting Equation (43), we have

\[
\begin{pmatrix}
\frac{du(t)}{dt} \\
\frac{dv(t)}{dt}
\end{pmatrix}
= L(\lambda) \begin{pmatrix} u \\ v \end{pmatrix} + \begin{pmatrix} f(u, v, \lambda) \\ g(u, v, \lambda) \end{pmatrix}, \tag{44}
\]

where

\[
f(u, v, \lambda) = 0 \tag{45}
\]

and

\[
g(u, v, \lambda) = \left[ -\frac{\beta}{(1 + \lambda)^3} + \frac{k(1 + \tau \lambda)}{(k + \lambda)^3} \right] v^2 - \frac{k}{(k + \lambda)^2} uv + \left[ \frac{\beta}{(1 + \lambda)^4} - \frac{k(1 + \tau \lambda)}{(k + \lambda)^4} \right] v^3 + \frac{k}{(k + \lambda)^3} uv^2 + o(|v|^4, |u||v|^2). \tag{46}
\]

In addition, let us define the matrix \( P \) as follows,

\[
P := \begin{pmatrix} 1 & 0 \\ N & M \end{pmatrix} \tag{47}
\]
with the following inverse

\[ P^{-1} := \begin{pmatrix} \frac{1}{N} & 0 \\ -\frac{M}{N} & \frac{1}{M} \end{pmatrix}, \]  

where

\[ M = -\frac{1}{\rho \tau} \omega(\lambda) = -\frac{1}{2\rho \tau} \sqrt{\frac{4h'(\lambda)\rho \lambda}{1 + \lambda} - \left(\frac{\lambda(1 + \tau \lambda)(1 - k)}{(1 + \lambda)(k + \lambda)^2} - \rho\right)^2} \]  

and

\[ N = \frac{1}{\rho \tau} (\psi(\lambda) + \rho) = \frac{1}{\rho \tau} \left[ \frac{\lambda(1 + \tau \lambda)(1 - k)}{2(1 + \lambda)(k + \lambda)^2} + \frac{1}{2} \rho \right]. \]  

When \( \lambda = \bar{\lambda} \), we have

\[ \bar{N} = \frac{1}{\tau}, \quad \bar{M} = -\frac{1}{\tau} \sqrt{\frac{\bar{\lambda}h'(. \bar{\lambda})}{(1 + \lambda)\rho}} = -\frac{1}{\tau} \sqrt{\frac{\tau \bar{\lambda}^2 + 2\tau k \bar{\lambda} + k + k \tau}{(1 + \bar{\lambda})(1 - k)}}, \]

\[ \omega(\bar{\lambda}) = \sqrt{\frac{\rho \bar{\lambda}h'(\bar{\lambda})}{1 + \bar{\lambda}}} = \frac{\bar{\lambda} \sqrt{(1 + \tau \bar{\lambda})(1 - k)(\tau \bar{\lambda}^2 + 2\tau k \bar{\lambda} + k + k \tau)}}{(1 + \bar{\lambda})(k + \bar{\lambda})^2}. \]  

Using the following transformation

\[ \begin{pmatrix} u \\ v \end{pmatrix} = P \begin{pmatrix} x \\ y \end{pmatrix}, \]

Equation (44) becomes

\[ \begin{pmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \end{pmatrix} = \tilde{L}(\lambda) \begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} F^1(x, y, \lambda) \\ F^2(x, y, \lambda) \end{pmatrix}. \]

Where \( \tilde{L}(\lambda) \) is defined as follows

\[ \tilde{L}(\lambda) := \begin{pmatrix} \psi(\lambda) & -\omega(\lambda) \\ \omega(\lambda) & \psi(\lambda) \end{pmatrix}. \]

Besides,

\[ F^1(x, y, \lambda) := 0 \]

and

\[ F^2(x, y, \lambda) := A_{02}y^2 + A_{11}xy + A_{12}xy^2 + A_{03}y^3 + o(|y|^4, |x||y|^3). \]

The coefficients in \( F^2(x, y, \lambda) \) are given by

\[ A_{02} := -\frac{M\beta}{(1 + \lambda)^3} + \frac{Mk(1 + \tau \lambda)}{(k + \lambda)^3}, \quad A_{11} := -\frac{2N\beta}{(1 + \lambda)^3} + \frac{2Nk(1 + \tau \lambda) - k(k + \lambda)}{(k + \lambda)^3}, \]

\[ A_{12} := \frac{3MN\beta}{(1 + \lambda)^4} + \frac{Mk(k + \lambda) - 3MNk(1 + \tau \lambda)}{(k + \lambda)^4}, \quad A_{03} := \frac{M^2\beta}{(1 + \lambda)^4} - \frac{M^2k(1 + \tau \lambda)}{(k + \lambda)^4}. \]  

(57)
Rewriting Equation (53) in polar coordinates, we have the following expressions

\[
\dot{r} = \psi(\lambda) r + a(\lambda) r^3 + \text{higher-order-terms},
\]

\[
\dot{\theta} = \omega(\lambda) + c(\lambda) r^2 + \text{higher-order-terms}.
\]  

(58)

Then, using Taylor expansion of Equation (58) at \( \lambda = \lambda \), we have

\[
\dot{r} = \psi'(\lambda)(\lambda - \lambda) r + a(\lambda) r^3 + o((\lambda - \lambda)^2 r, (\lambda - \lambda)^3 r^2, r^3),
\]

\[
\dot{\theta} = \omega(\lambda) + \omega'(\lambda)(\lambda - \lambda) r + o((\lambda - \lambda)^2 r^2, (\lambda - \lambda)^3 r^2, r^4).
\]  

(59)

Using [9,28], we determine the stability of the periodic solution. In particular, we determine the sign of \( a(\lambda) \), where \( a(\lambda) \) is given by

\[
a(\lambda) := \frac{1}{16} \left[ F_{xxx}^1 + F_{xxy}^1 + F_{xyy}^2 + F_{yyy}^2 \right] + \frac{1}{16\omega(\lambda)} \left[ F_{xy}^1 (F_{xx}^1 + F_{xy}^1) - F_{xy}^2 (F_{x}^2 + F_{yy}^2) - F_{xx}^1 F_{xx}^2 + F_{xy}^1 F_{yy}^2 \right].
\]  

(60)

We note that all the partial derivatives of \( F \) are evaluated at \((x, y, \lambda) = (0, 0, \lambda)\). It is easy to determine that \( F_{xxx}^1(0, 0, \lambda) = F_{xxy}^1(0, 0, \lambda) = F_{xyy}^1(0, 0, \lambda) = F_{xx}^1(0, 0, \lambda) = F_{xy}^1(0, 0, \lambda) = F_{yy}^1(0, 0, \lambda) = 0 \), and that

\[
F_{xxx}^2 = \frac{6\beta N^2}{(1 + \lambda)^4} + \frac{2kN[2k + 2\lambda - 3N(1 + \tau\lambda)]}{(k + \lambda)^4},
\]

\[
F_{xxy}^2 = \frac{2N\beta}{(1 + \lambda)^3} + \frac{2Nk(1 + \tau\lambda) - k(k + \lambda)}{(k + \lambda)^3},
\]

\[
F_{xyy}^2 = \frac{2M\beta}{(1 + \lambda)^3} + \frac{2Mk(1 + \tau\lambda)}{(k + \lambda)^3}.
\]  

(61)

Hence,

\[
a_0 := a(\lambda) = \frac{1}{16} \left[ F_{xxy}^2 + F_{xyy}^2 \right] + \frac{1}{16\omega(\lambda)} \left[ -F_{xy}^2 (F_{xx}^2 + F_{yy}^2) \right]
\]

\[
= \frac{3\beta (k + \lambda)^4 - k(1 + \tau\lambda)(1 + \lambda)^2 (2k + 1)}{8\tau(1 + \tau\lambda)(1 - k)(1 + \lambda)^3(k + \lambda)}
\]

\[
+ \frac{2\beta (k + \lambda)^3 + k(k\tau - \tau\lambda - 2)(1 + \lambda)^3}[\beta (k + \lambda)^2 - k(1 + \tau\lambda)(1 + \lambda)^2]
\]

\[
\frac{1}{8\tau^2(1 + \tau\lambda)(2k + 1)(k + \lambda)^2}.
\]  

(62)

This completes the proof.

\[\blacksquare\]

Theorem 4.5: Suppose that \( k \geq 1 \) and \( R_0 = \beta k > 1 \). Then, the unique positive steady state solution \( \mathcal{E}_\lambda = (u_\lambda, v_\lambda) \) of system (2) is globally asymptotically stable for \( \lambda \in (0, \infty) \).
**Proof:** We define the Lyapunov function as:

\[ V(u, v) = B(u) + A(v), \]  

(63)

where

\[ B(u) = \frac{1}{\rho \tau} \int (u - u^*) \, du, \quad A(v) = \int \frac{k + v}{v} (v - v^*) \, dv. \]  

(64)

Then,

\[
\frac{\partial V}{\partial t}(u, v) \bigg|_{(2)} = \frac{dB}{du} \cdot \frac{du}{dt} + \frac{dA}{dv} \cdot \frac{dv}{dt} = \frac{dB}{du} \rho (1 + \tau v - u) + \frac{dA}{dv} \left( \frac{\beta v}{1 + v} - \frac{uv}{k + v} \right).
\]

(65)

Because

\[ 1 + \tau v^* - u^* = \frac{\beta}{1 + v^*} - \frac{u^*}{k + v^*} = 0, \]  

(66)

we have

\[
\frac{\partial V}{\partial t}(u, v) \bigg|_{(2)} = \frac{dB}{du} \rho \left[ (1 + \tau v - u) - (1 + \tau v^* - u^*) \right] + \frac{dA}{dv} \left[ \left( \frac{\beta}{1 + v} - \frac{u}{k + v} \right) - \left( \frac{\beta}{1 + v^*} - \frac{u^*}{k + v^*} \right) \right] 
\]

\[
= \frac{dB}{du} \rho \left[ \tau (v - v^*) - (u - u^*) \right] - \frac{dA}{dv} \frac{\beta (v - v^*)}{(1 + v)(1 + v^*)} 
\]

\[
- \frac{dA}{dv} \left[ \frac{k(u - u^*)}{(k + v^*)(k + v)} - \frac{u^*(v - v^*)}{(k + v^*)(k + v)} \right] + \frac{v^*(u - u^*)}{(k + v^*)(k + v)}.
\]

(67)

If \( k = 1 \), after some calculations, we have,

\[
\frac{\partial V}{\partial t}(u, v) \bigg|_{(2)} = -\frac{1}{\tau} (u - u^*)^2 - \frac{\beta - u^*}{1 + v^*} (v - v^*)^2 = -\frac{1}{\tau} (u - u^*)^2,
\]

(68)

where we use the fact that \( \beta = u^* \) when \( k = 1 \). Hence, we conclude that \( (\partial V/\partial t)(u, v) \big|_{(2)} < 0 \). In this case, the endemic equilibrium \( E^*_\lambda = (u^*_\lambda, \lambda) \) of system (2) is globally asymptotically stable. In addition, If \( k > 1 \), after some simplifications, we have

\[
\frac{\partial V}{\partial t}(u, v) \bigg|_{(2)} = -\frac{1}{\tau} (u - u^*)^2 - \frac{\beta (k + v)(v - v^*)^2}{(1 + v)(1 + v^*)} + \frac{u^*(v - v^*)^2}{k + v^*}
\]

\[
= -\frac{1}{\tau} (u - u^*)^2 - \frac{(v - v^*)^2 (\beta (k + v)(k + v^*) - u^*(1 + v)(1 + v^*))}{(1 + v)(1 + v^*)(k + v^*)}.
\]

(69)

Using Equation (66), we have \( \beta = (1 + v^*)u^*/(k + v^*) \). Hence, we can easily check that \( \beta (k + v)(k + v^*) - u^*(1 + v)(1 + v^*) > 0 \) for \( k > 1 \). Thus, we conclude that \( (\partial V/\partial t)(u, v) \big|_{(2)} < 0 \), which implies that the endemic equilibrium \( E^*_\lambda = (u^*_\lambda, \lambda) \) of system (2) is globally asymptotically stable. This completes the proof. ■
Corollary 4.6: Suppose that $k \geq 1$ holds. Then the following statements hold:

1. If $R_0 = \beta k \leq 1$, then the semi-trivial steady state $(1, 0)$ is globally asymptotically stable.
2. If $R_0 = \beta k > 1$, then the unique positive steady state solution $(u_\lambda, v_\lambda)$, with $\lambda \in (0, \infty)$, of system (2) is globally asymptotically stable.

The proof of the above corollary is easy and has been ignored. The Corollary 4.6(1) follows from the use of inequalities and comparison technique, where we can use the fact that $k \geq 1$ and $R_0 \leq 1$, which imply that $\beta \leq 1$. Corollary 4.6(2) is essential the same as Theorem 4.5.

In addition, for completeness, we also discuss the boundedness of the solution of system (2) and the existence of limit cycles in $\Omega$, and obtain the following theorems.

Theorem 4.7: Suppose that $0 < k < 1$. Then, all solutions $(u(t), v(t))$ of the system (2) are bounded.

Proof: We consider the following auxiliary system

$$
\begin{align*}
\tilde{u}_t &= \rho (1 + \tau \tilde{v} - \tilde{u}), \quad t > 0, \\
\tilde{v}_t &= \frac{\beta \tilde{v}}{1 + \tilde{v}} - \frac{\tilde{u} \tilde{v}}{1 + \tilde{v}}, \quad t > 0, \\
\tilde{u}(0) &= u_0 > 0, \quad \tilde{v}(0) = v_0 > 0.
\end{align*}
$$

By Theorem 4.5, it follows that the solution $(\tilde{u}(t), \tilde{v}(t))$ of system (70) converges to $(u_\lambda, \lambda)$ globally. Because $0 < k < 1$, we have

$$
\frac{\beta v}{1 + v} - \frac{uv}{k + v} < \frac{\beta v}{1 + v} - \frac{uv}{1 + v}.
$$

Hence, by comparison principle, we have

$$
u(t) \leq \tilde{u}(t), \quad v(t) \leq \tilde{v}(t).
$$

This together with the global stability of $(u_\lambda, \lambda)$ indicates that $(u(t), v(t))$ of system (2) is bounded. This completes the proof.

Theorem 4.8: If $\rho \geq \beta$, then the system (2) does not admit closed orbit in $\Omega$.

Proof: To show that the system does not have periodic orbits or limit cycles, we observe that,

$$
\begin{align*}
\int \int \frac{\partial}{\partial u} (\rho (1 + \tau v - u)) + \frac{\partial}{\partial v} \left( \frac{\beta v}{1 + v} - \frac{uv}{k + v} \right) du dv \\
= \int \int -\rho + \frac{\beta}{(1 + v)^2} - \frac{uk}{(k + v)^2} du dv = \int \int \frac{\beta - \rho (1 + v)^2}{(1 + v)^2} - \frac{uk}{(k + v)^2} du dv \\
= \int \int \frac{(\beta - \rho) (1 + 2v + v^2)}{(1 + v)^2} - \frac{uk}{(k + v)^2} dv < 0,
\end{align*}
$$

provided that $\beta - \rho \leq 0$. Hence, there is no closed orbit in $\Omega$. This completes the proof.
5. Discussion

In this paper, we have considered a mathematical model describing the bacterial infection of a homogeneous tissue. Our analysis of the model has shown the existence of a bacteria-free and two endemic compromised steady states. By using steady state analysis and Hopf bifurcation theory, we show the existence of saddle-node connections and limit cycles. In this section, we discuss our analytic results and its biological implication.

In the case where the ratio of inhibition effects of increased bacterial density on its growth to that of phagocytosis is greater or equal to one (i.e. $k \geq 1$), the model exhibit two possible situations. When $\mathcal{R}_0 = \beta k \leq 1$, the bacteria-free equilibrium is globally asymptotically stable. That is, whenever $\mathcal{R}_0 \leq 1$, the elimination of bacterial infection is always sustained after initial transient proliferation of infection. The infection-free steady state is unstable when $\mathcal{R}_0 > 1$, and one of the endemic compromise steady state (i.e. the endemic compromise steady state $E_\lambda$) emerges and becomes globally asymptotically stable. The bacteria proliferates gradually before stabilizing to a positive steady state. Figure 1 shows the two possible dynamical features present in the model for $k \geq 1$. This case corresponds to the existence of forward bifurcation. In particular, when $\mathcal{R}_0 \leq 1$, the system approaches the bacteria-free equilibrium which is globally asymptotically stable (see Figure 1(a)); when $\mathcal{R}_0 > 1$, the bacteria-free equilibrium is unstable and model converges to the unique endemic equilibrium (see Figure 1(b)).

For $k < 1$, the dynamical features are more involved. In particular, we observed that when $k \geq 1/(1 + \tau)$, the model exhibits forward bifurcation with unique endemic equilibrium and when $k < 1/(1 + \tau)$ the system can have backward bifurcation where there are two endemic equilibria. Unlike their counterparts in standard epidemic models, these

![Figure 1](image-url)
Figure 2. Temporal Dynamics: The model (2) shows the dynamics of the bacteria-free solution when $R_0 \leq 1$ in panel (a) with the following parameter values $\rho = 2, \tau = 1.5, \beta = 1, k = 0.5$; and shows the stable dynamic of the unique endemic solution when $R_0 > 1$ in panel (b) with the following parameter values $\rho = 2, \tau = 1.5, \beta = 4, k = 0.5$. Here $1/(1 + \tau) < k < 1$ and $\rho > A(\lambda_{**})$ (see Theorem 4.3). Matlab ode45 solver is used to solve system (2) with initial conditions $v(0) = 1$ and $u(0) = 0.2$.

steady state bifurcations structures showed quite interesting dynamical behaviours. For example, in the case of forward, the unique endemic equilibrium can lose stability or can be globally asymptotically stable depending on other secondary conditions on the parameters; and similar results are observed in the case of backward bifurcation.

For $1/(1 + \tau) < k < 1$, we observe that the endemic compromise steady state $E_{\lambda}$ is globally asymptotically stable for all $\lambda$ if and only if $\rho > A(\lambda_{**})$. The dynamic features of the steady state is similar to those observed in Figure 1, and the steady-state bifurcation is also similar (see Figure 2). However, when $1/(1 + \tau) < k < 1$ and $\rho < A(\lambda_{**})$, additional dynamical patterns can be observed. In particular, $E_{\lambda}$ is globally asymptotically stable for any $\lambda \in (0, \lambda_1) \cup (\lambda_2, \infty)$ if $\rho < A(\lambda_{**})$. That is, for $1 < R_0 < R_1$ and $R_0 > R_1 > 1$, the endemic equilibrium $E_{\lambda}$ is globally asymptotically stable. Moreover, if $\rho < A(\lambda_{**})$, the endemic equilibrium $E_{\lambda}$ is unstable for $\lambda \in (\lambda_1, \lambda_2)$ (i.e. $R_0 \in (R_1, R_2)$) and undergoes Hopf bifurcation, where $\lambda = \lambda_1$ and $\lambda = \lambda_2$ are Hopf points. It should noted in this case, the bacteria has similar conditional property as in the previous discussion, i.e. when $R_0 \leq 1$ the bacteria-free equilibrium is globally stable and unstable when $R_0 > 1$. Here the forward bifurcation structure is different from the previous bifurcation for $k \geq 1$, for the unique endemic equilibrium can be stable or unstable depending value of $R_0$ when $R_0 > 1$. In particular, two additional thresholds are needed (see Theorem 4.3(1)). Let $R_c$ such that $\lambda = \lambda_0$ and let define $R_1$ and $R_2$ be such that $\rho$ values give $\lambda = \lambda_1$ and $\lambda = \lambda_2$, respectively, where $\lambda_1$ and $\lambda_2$ are the solution of $A(\lambda) = \rho$ (see Theorem 4.3). Then, the unique endemic equilibrium is asymptotically stable provided that $\lambda \notin (\lambda_1, \lambda_2)$. In other words, when $1 < R_1 < R_0 < R_2$, the endemic equilibrium is unstable and the system exhibits oscillatory behaviours, $R_0 = R_1$ (e.g. $\lambda = \lambda_1$) and $R_0 = R_2$ ($\lambda = \lambda_2$) are
Figure 3. Temporal Dynamics: The model (2) shows the dynamics of the bacteria-free solution when $R_0 \leq 1$ in panel (a) with the following parameter values $\rho = 0.2, \tau = 1.5, \beta = 1, k = 0.5$; shows the dynamic feature of the unique endemic solution when $R_0 > 1$ in panel (b) with the following parameter values $\rho = 0.2, \tau = 1.5, \beta = 2.15, k = 0.5$; shows the stable dynamic of the unique endemic solution when $R_0 > 1$ in panel (c) with the following parameter values $\rho = 0.2, \tau = 1.5, \beta = 2.5, k = 0.5$ where the system undergoes Hopf bifurcation. Here $1/(1+\tau) < k < 1$ and $\rho < A(\lambda^{**})$ (see Theorem 4.3). Matlab ode45 solver is used to solve system (2) with initial conditions $v(0) = 1$ and $u(0) = 0.2$.

Hopf bifurcation points. Figure 3 shows the three different dynamic behaviours, where (see Figure 3(c)).

For $k < 1/(1+\tau) < 1$, we have two endemic steady states namely, $E_{\lambda}$ and $E_{\mu}$. In addition, the endemic equilibrium $E_{\mu}$ is always unstable, and the stability of $E_{\lambda}$ depends on the parameters. In particular, $E_{\lambda}$ is locally asymptotically stable for $\lambda \in (\lambda^{**}, \infty)$ if
rate (e.g. maximum bacterial growth rate) is smaller relative to the maximum leukocyte phagocytosis rate, and the initial conditions determine which equilibrium is selected. When $R_0 > 1$, $E_\lambda$ is globally asymptotically stable, and $E_0$ is unstable; and there is no Hopf bifurcation (see similar behaviours are shown in Figures 1–2). For the second case, we have that $R_c < R_0 < 1$ and $\lambda_0 < \lambda_1 < \lambda_2$. When $R_0 < R_c < 1$, $E_0$ is again globally asymptotically stable, and unstable when $R_0 > 1$. For $R_0 > 1$, both $E_0$ and $E_\lambda$ are locally asymptotically stable and the initial conditions again determine which steady-state is selected. When $R_c < R_0 < 1$, both $E_0$ and $E_\lambda$ are unstable; and $E_0$ remains unstable for $R_0 > 1$. For $R_0 > R_2 > 1$, endemic $E_\lambda$ is globally asymptotically stable. At $R_0 = R_1$ and $R_0 = R_2$, the endemic equilibrium $E_\lambda$ undergoes Hopf bifurcation (see similar dynamical behaviours are shown in Figure 3(c)). The results are equivalent to condition in Theorem 4.3 when $\lambda_0 < \lambda_1 < \lambda_2$ where at $\lambda = \lambda_1$ and $\lambda = \lambda_2$ the system (2) undergoes Hopf bifurcations (see similar dynamical behaviours are shown in Figure 3(c)). For the third and final scenario, we note that $\lambda_1 < \lambda_0 < \lambda_2$ and $R_c < R_1 < 1 < R_2$. When $R_c < R_1 < R_0 < 1$, the bacteria-free is again globally asymptotically stable and unstable if $R_0 > 1$; and the system (2) undergoes Hopf bifurcations only at $\lambda = \lambda_2$ and $R_0 = R_2$ (see similar dynamical behaviours are shown in Figure 3(c)). For $R_0 > R_2 > 1$, the endemic equilibrium $E_\lambda$ is globally asymptotically stable.

In previous discussion, we have focused mostly on the dynamic behaviours of the model under different conditions, which mostly depend on the values of four key dimensionless parameters $\rho$, $\beta$, $\tau$ and $k$, where $\rho$ is the ratio of leukocyte death rate to maximum phagocytosis rate, $\tau$ represents ratio of enhanced phagocyte emigration rate to normal emigration rate, $\beta$ denotes the ratio of maximum bacterial growth rate to maximum leukocyte phagocytosis rate, and $k$ is ratio of inhibitory effect of increasing bacteria density on bacterial growth to inhibitory effect of phagocytosis rate. On one hand, suppose that scale measuring the inhibitory effects of bacterial density on its growth relative to phagocytosis rate is greater or equal to one ($k \geq 1$). Then, we observe that only two possible outcomes can be seen, in which the bacterial infection is eliminated or is permanent. For instance, when the maximum bacterial growth rate is smaller relative to the maximum leukocyte phagocytosis rate (e.g. $\beta = 0.2$) such that $R_0 < 1$ as shown in Figure 1, the bacterial infection cannot persist, and leukocytes lead to elimination of these infections. However, when the maximum bacterial growth rate is greater than the maximum leukocyte phagocytosis rate (e.g. $\beta = 2$), the leukocytes are unable to effective eliminate the bacterial infection, and therefore, there is a persistence of endemic compromised disease state and the reproductive success of the infection is greater than one (i.e. $R_0 > 1$).

On the other hand, when the inhibitory effects of bacterial density on its growth relative to phagocytosis rate is less than one ($k < 1$), the system exhibits two types of steady-state
behaviours, whose dynamic features are dependent on whether $1/(1 + \tau) < k < 1$ or $k < 1/(1 + \tau) < 1$. In particular, when $1/(1 + \tau) < k < 1$, and the ratio of leukocyte death rate to phagocytosis rate ($\rho$) is greater than a threshold condition (i.e. $\rho > A(\lambda_{**}) := \rho_*$), we observe similar dynamic features as in the case of Figure 1 (see Figure 2), where the bacterial infection is always eliminated or persists, depending on the reproduction success $\mathcal{R}_0$. For $\mathcal{R}_0 < 1$, the bacterial infection is always eliminated, and for $\mathcal{R}_0 > 1$, the compromise state is permanent. However, when the ratio of leukocyte death rate to phagocytosis rate ($\rho$) is less than a threshold condition (e.g. $\rho < \rho_*$), bacterial infection is always eliminated whenever $\mathcal{R}_0 < 1$. But, when $\mathcal{R}_0 > 1$, the disease is always permanent. In addition, there exists regions, depending on the initial bacterial density, where the infection always approaches a steady state or oscillates around the endemic compromise solution.

For $k < 1/(1 + \tau) < 1$, the system exhibits backward bifurcation where the smaller endemic compromise steady state is always unstable. The stability of the larger endemic equilibrium depends on various parameter thresholds. In particular, when the ratio of leukocyte death rate to phagocytosis rate ($\rho$) is greater than a threshold condition (i.e. $\rho > A(\lambda_{**}) := \rho_*$), we observe standard backward bifurcation where the larger endemic compromise steady state is stable where the bacterial infection persists for all initial condition whenever $\mathcal{R}_0 > 1$. For $\mathcal{R}_0 < 1$, the bacterial can either be eliminated or can persist, where reducing $\mathcal{R}_0$ below one is no longer effective. When $\rho < \rho_*$, the larger compromise endemic steady state can approach to an equilibrium or oscillate around the equilibrium for some parameter values (see Figure 3). All these behaviours are seen within the biological ranges of the parameters obtained in the literature.

6. Conclusion

In this paper, we provide a rigorous mathematical analysis of a model describing the bacterial infection of a homogeneous tissue. In particular, we presented steady-state analysis of all the equilibria, namely bacterial infection-free and two endemic compromised steady states. We showed a threshold-like condition for the existence and stability of each of the equilibria, where the bacteria-free equilibrium is globally asymptotically stable whenever $k \geq 1$, when $\mathcal{R}_0 = \beta k \leq 1$, and is unstable when $\mathcal{R}_0 > 1$. Similar results were established for both of the endemic compromise equilibria, where one of the endemic equilibria is always unstable, and the dynamic property of the second endemic equilibrium is very rich, where different dynamic behaviours can be observed. In particular, we showed that the model exhibits rich dynamic features, including the existence of bubble bifurcation and Hopf bifurcation. Moreover, we showed the existence of saddle-node connections and limit cycles. In this paper, we did not show the uniqueness of the limit cycle, and we leave this analysis as an open problem. Using parameter values obtained from literature, we simulated various dynamic behaviours predicted by our analysis.

Acknowledgments

The authors wish to thank the Editor and the reviewers for their valuable comments and suggestions that greatly improved the presentation of this work.
Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] R.B. Allan and P.C. Wilkinson, A visual analysis of chemotactic and chemokinetic locomotion of human neutrophil leucocytes, Exp. Cell Res. 111 (1978), pp. 191–203.
[2] W. Alt and D.A. Lauffenburger, Transient behavior of a chemotaxis system modelling certain types of tissue inflammation, J. Math. Biol. 24 (1987), pp. 691–722.
[3] C.G. Craddock, Production, distribution, and fate of Granulocytes, in Hematology, W.J. Williams, E. Beutler, A.J. Erslav, and R.W. Rundles, eds., McGraw-Hill, New York, 1972, pp. 607–618.
[4] J.L. Dunster, H.M. Byrne, and J.R. King, The resolution of inflammation: A mathematical model of neutrophil and macrophage interactions, Bull Math Biol. 76 (2014), pp. 1953–1980.
[5] A.S. Elragig, On transients, Lyapunov functions and Turing instabilities, Ph.D. diss., University of Exeter, 2013.
[6] E.S. Fisher and D.A. Lauffenburger, Analysis of the effects of immune cell motility and chemotaxis on target elimination dynamics, Math. Biosci. 98 (1990), pp. 73–102.
[7] R. M. Ford and D. A. Lauffenburger, Analysis of chemotactic bacterial distributions in population migration assays using a mathematical model applicable to steep or shallow attractant gradients, Bull. Math. Biol. 53 (1991), pp. 721–749.
[8] P.T. Foteinou, S.E. Calvano, S.F. Lowry, and I.P. Androulakis, Modeling endotoxin-induced systemic inflammation using an indirect response approach, Math. Biosci. 217 (2009), pp. 27–42.
[9] B.D. Hassard, N.D. Kazarinoff, and Y.H. Wan, Theory and Application of Hopf Bifurcation, Cambridge University Press, Cambridge, 1981.
[10] T. Hau, R. Hoffman, and R.L. Simmons, Mechanism of the adjuvant effect of hemoglobin in experimental peritonitis: I. In vivo inhibition of peritoneal leukocytosis, Surgery 83 (1978), pp. 223–229.
[11] Z. Jing, Qualitative analysis of a mathematical model for tissue inflammation dynamics, Acta Math. Sinica 3 (1987), pp. 327–339.
[12] J.A. Johnson, Capillary permeability, extracellular space estimation, and lymph flow, Amer. J. Physiol.211 (1966), pp. 1261–1263.
[13] M. Klempner and S. Wolff, The neutrophil in host defense: Congenital, acquired, and drug-induced abnormalities, in Infections in the Abnormal Host, M.H. Griece, eds., Yorke Medical Books, New York, 1980, pp. 11–37.
[14] D.A. Lauffenburger, Effects of motility and chemotaxis in cell population dynamical systems, Ph.D. diss., University of Minnesota, 1979.
[15] D.A. Lauffenburger, Mathematical model for tissue inflammation: Effects of spatial distribution, cell motility, and chemotaxis, Lecture Notes in Riomathematics, Vol. 38, 1980, pp. 397–409.
[16] D.A. Lauffenburger and C.R. Kennedy, Analysis of a lumped model for tissue inflammation dynamics, Math. Biosci. 53 (1981), pp. 189–221.
[17] D.A. Lauffenburger and C.R. Kennedy, Localized bacterial infection in a distributed model for tissue inflammation, J. Math. Biol. 16 (1983), pp. 141–163.
[18] D. Lauffenburger and K.H. Keller, Effects of leukocyte random motility and chemotaxis in tissue inflammatory response, J. Theor. Biol. 81 (1979), pp. 475–503.
[19] P.D.J. Leijh, M.T. van den Barselaar, T.L. van Zwet, I. Dubbleman-Rempt, and R. van Furth, Kinetics of phagocytosis of Staphylococcus oureus and Escherichia coli by human granulocytes, Immunology 37 (1979), pp. 453–465.
[20] E.N. Lightfoot, Transport Phenomena and Living Systems, John Wiley, New York, 1974.
[21] E. Metchnikoff, Lectures on the Comparative Pathology of Inflammation, Dover, New York, 1968.
[22] M. Mimura and T. Tsujikawa, Aggregating pattern dynamics in a chemotaxis model including growth, Phys. A 230 (1996), pp. 499–543.
[23] K.J. Painter, P.K. Maini, and H.G. Othmer, Development and applications of a model for cellular response to multiple chemotactic cues, J. Math. Biol. 41 (2000), pp. 285–314.
[24] T.P. Stossel, Quantitative studies of phagocytosis: Kinetic effects of cations and heat-labile opsonin, J. Cell Biol. 58 (1973), pp. 346–356.
[25] M.J. Tindall, P.K. Maini, S.L. Porter, and J.P. Armitage, Overview of mathematical approaches used to model bacterial chemotaxis II: Bacterial populations, Bull. Math. Biol. 70 (2008), pp. 1570–1607.
[26] M.J. Tindall, E.A. Gaffney, P.K. Maini, and J.P. Armitage, Theoretical insights into bacterial chemotaxis, Wiley Interdiscip. Rev. 4 (2012), pp. 247–259.
[27] P.C. Wilkinson, Chemotaxis and Inflammation, Churchill-Livingstone, London, 1974.
[28] F. Yi, J. Wei, and J. Shi, Diffusion-driven instability and bifurcation in the Lengyel-Epstein system, Nonlinear Anal. 9 (2008), pp. 1038–1051.
[29] M. Zhu and J.D. Murray, Parameter domains for generating spatial pattern: A comparison of reaction-diffusion and cell chemotaxis models, Int. J. Bifurcat. Chaos 5 (1995), pp. 1503–1524.