BIFURCATION ANALYSIS FOR AN IN-HOST MYCOBACTERIUM TUBERCULOSIS MODEL

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Dedicated to Professor Sze-Bi Hsu on the occasion of his 70th birthday

Abstract. Tuberculosis infection is still a major threat to humans and it may progress slowly or rapidly to clearance, latent infection, or active disease. In this paper, considering T cells can perform acceleration effect on their own recruitment, an in-host model of Mycobacterium tuberculosis is studied. Focus type and elliptic type of nilpotent singularities of codimension 3 are analyzed in this four dimensional model. Complex dynamical behaviors such as homoclinic loop, saddle-node bifurcation of limit cycle and co-existence of two limit cycles are revealed by bifurcation analysis. Especially, the slow-fast periodic solution with large-amplitude or small-amplitude is observed in numerical simulations, which provides a perfect explanation for the reactivation of latent infection.

1. Introduction. Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb), and one of the top ten causes of death, surpassing even AIDS [26]. About 25% of the world’s population is infected with Mtb [27], and most of the infected individuals develop into latent infection. Depending on the course of Mtb infection in host, latent infection may extend for the whole lifetime or be reactivated and progress to active disease [10]. Thus, it is of great significance to study the mechanism of Mtb infection in host and there have been numerous researches (see [7, 18] and the references cited therein). In the host, Mtb is confined to the site of infection known as granuloma, a collection of macrophages, T lymphocytes and fibroblasts, as well as Mtb [8]. In granuloma, Mtb is absorbed by macrophages. However, Mtb can greatly reduce the bactericidal ability of macrophages and even be able to resist lysozyme and reproduce in macrophages. After multiplying to a certain extent in macrophages, Mtb can induce macrophages to rupture so that more free Mtb is released out [15, 18]. To eliminate Mtb, the infected macrophages induce the adaptive immune response through presenting antigen molecules to T cells. Then T cells are activated and recruited into the granuloma. Through secreting cytokines, these activated T cells can help to kill the infected macrophages and intracellular Mtb [23, 24].

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Various mathematical models have been applied to understand the dynamics of Mtb [5, 11, 13, 14, 17, 22, 25, 29]. Recently, considering the principal features of cellular immunology against Mtb and the new discovery that Mtb can grow vigorously in the micro-environment of granulomas, Ibarguen-Mondragon et al. [13] extended their previous studies [14] and established a model as follows:

\[
\begin{align*}
\frac{dM_U}{dt} &= \Lambda - \mu_U M_U - \beta M_U B, \\
\frac{dM_I}{dt} &= \beta M_U B - \sigma M_I - \alpha T M_I, \\
\frac{dB}{dt} &= N\sigma M_I + vB \left(1 - \frac{B}{K}\right) - \delta M_U B - \mu_B B, \\
\frac{dT}{dt} &= k_I \left(1 - \frac{T}{T_{\text{max}}}\right) M_I - \mu_T T.
\end{align*}
\]  

Here, \(M_U(t)\), \(M_I(t)\), \(B(t)\) and \(T(t)\) represent the densities of normal macrophages, infected macrophages, extracellular Mtb and T cells respectively. \(\Lambda\) denotes the recruitment rate of normal macrophages, \(\mu_U\), \(\mu_B\), \(\mu_T\) represent the per capital death rate of the normal macrophages, Mtb and T cells respectively, and \(\sigma\) denotes the apoptosis rate of infected macrophages caused by Mtb. Normal macrophages are infected by Mtb with rate \(\beta\), infected macrophages are eliminated by T cells at a rate \(\alpha\), and Mtb are eliminated by normal macrophages at a rate \(\delta\). \(N\sigma M_I\) represents the total number of free Mtb released by infected macrophages, \(vB(1 - B/K)\) denotes the extracellular proliferation of \(B\). T cells are recruited at a rate \(k_I\), and \(T_{\text{max}}\) is the maximum T cell population level.

They discovered, in [13, 14], an S-shaped bifurcation and showed that there may be up to three bacteria-present equilibria, two locally asymptotically stable, and one unstable, which gives a reasonable explanation why Mtb infection can cause latent infection or active diseases. Note that the recruitment term of T cells is \(k_I M_I(1 - T/T_{\text{max}})\), which means that T cells show inhibition effect on their own recruitment. This is the case when T cells tend to be saturated. However, many studies have shown that the memory function of T cells can perform acceleration effect on their own recruitment and T cells tend to increase linearly in the early stage of Mtb infection [7, 19, 20, 23]. And Flynn [7] also showed that the recruitment of T cells starts after the activation of T cells which requires the interaction between T cells and the antigen molecules presented by macrophages. Hence, it is more reasonable to use the bilinear function \(\rho T M_I\) to denote the recruitment of T cells. Considering these factors, we establish the following model:

\[
\begin{align*}
\frac{dM_U}{dt} &= \Lambda - \mu_U M_U - \beta M_U B, \\
\frac{dM_I}{dt} &= \beta M_U B - (\sigma + \mu_I) M_I - \alpha T M_I, \\
\frac{dB}{dt} &= N\sigma M_I + vB \left(1 - \frac{B}{K}\right) - (\theta \beta + \delta) M_U B - \mu_B B, \\
\frac{dT}{dt} &= \rho T M_I - \mu_T T,
\end{align*}
\]  

where \(\rho\) is a positive constant, the term \(\theta \beta M_U B\) means that extracellular Mtb \(B\) becomes intracellular Mtb by infecting macrophage and \(\mu_I\) represents the mortality
of infected macrophages through autophagy [1]. According to biological background [17], we assume $\mu_U < \sigma$.

In this paper, we systematically study the bifurcations of model (2) by rigorous mathematical analysis and show that the bilinear recruitment function of T cells leads to more complex dynamical behaviors. Firstly, we find that system (2) has a stable immune-free equilibrium when the reproduction number of immune response $R_1$ is less than unity, which illustrates that people with weak or deficient acquired immunity are more likely to develop active tuberculosis [7]. Furthermore, comparing to [5, 11, 13, 22, 29], there emerge bifurcation phenomena such as homoclinic bifurcation, Bogdanov-Takens bifurcation of codimension 2 and 3 and saddle-node bifurcation of limit cycle. These findings provide more insights how the latency can be a dynamic process and may rapidly progress to reactivation by a large oscillation, and how a slow-fast periodic solution mimics the progression of the disease which stays long in the low infection status and then reaches a high infection status, as advocated by [8, 16] for tuberculosis.

This paper is organized as follows. In the next section, we analyze the existence and stability of boundary equilibria and explore bifurcations of the boundary equilibria. In Section 3, we study the existence of positive equilibria and focus on bifurcation analysis. We show that Bogdanov-Takens bifurcation of codimension 2 and 3 occur in our model. Numerical results in Section 4 are presented to find more interesting dynamical behaviors. The paper ends with a brief discussion in Section 5.

2. Analysis of boundary equilibria. In this section, we study the existence and types of boundary equilibria and explore bifurcations from the boundary equilibria. Before this, considering the biological backgrounds, we introduce the following region,

$$\Omega = \left\{ (M_U, M_I, B, T) \in \mathbb{R}^4_+ : M_U + M_I \leq \frac{\Lambda}{\mu_U}, B \leq \Gamma, M_U + \frac{\rho T}{\alpha} \leq \frac{\Lambda\beta\Gamma}{M\mu_U} \right\},$$

$$\Gamma = \frac{K(v - \mu_B) + \sqrt{K^2(v - \mu_B)^2 + 4vKN\sigma\frac{\Lambda}{\mu_U}}}{2v}, \quad M = \min\{\sigma + \mu_I, \mu_T\}.$$  

It is easy to get that $\Omega$ is a positively invariant set for all solutions of (2) that initiate in the first octant.

It is clear that system (2) has a unique infection-free equilibrium $E_0(\Lambda/\mu_U, 0, 0, 0)$. Using the survival function method [12], we obtain the basic reproduction number of Mtb:

$$R_0 = \frac{N\sigma\beta\Lambda + v\mu_U(\sigma + \mu_I)}{((\theta\beta + \delta)\Lambda + \mu_B\mu_U)(\sigma + \mu_I)}. \quad (3)$$

For the stability of infection-free equilibrium $E_0$, we state following theorem.

**Theorem 2.1.** The infection-free equilibrium $E_0$ is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.

*Proof.* The Jacobian matrix of system (2) at $E_0$ is

$$J(E_0) = \begin{pmatrix}
-\mu_U & 0 & -\frac{\Lambda\beta}{\mu_U} & 0 \\
0 & -(\sigma + \mu_I) & \frac{\Lambda\beta}{\mu_U} & 0 \\
0 & N\sigma & v - \mu_B - \frac{\Lambda(\theta\beta + \delta)}{\mu_U} & 0 \\
0 & 0 & 0 & -\mu_T
\end{pmatrix}. \quad (4)$$


Its characteristic equation is
\[ 0 = (\lambda + \mu_U)(\lambda + \mu_T) \left[ \lambda^2 + \left( \sigma + \mu_1 + (\theta \beta + \delta) \frac{\Lambda}{\mu_U} + \mu_B - v \right) \lambda 
+ (\sigma + \mu_1)(1 - R_0) \left( \theta \beta + \delta \right) \frac{\Lambda}{\mu_U} + \mu_B \right] . \] (5)

If \( R_0 < 1 \), then all roots of (5) have negative real parts. If \( R_0 > 1 \), (5) has one positive root. Thus \( E_0 \) is locally asymptotically stable if \( R_0 < 1 \) and is unstable if \( R_0 > 1 \).

Next, let us consider the immune-free equilibria of system (2). An equilibrium \( \tilde{E}(M_U, M_I, B, 0) \) satisfies:
\[ \begin{align*}
\Lambda - \mu_U M_U - \beta M_U B &= 0, \\
\beta M_U B - (\sigma + \mu_1) M_I &= 0, \\
N \sigma M_I + v B \left( 1 - \frac{B}{K} \right) - (\theta \beta + \delta) M_U B - \mu_B B &= 0.
\end{align*} \] (6)

It follows that
\[ M_U = \frac{\Lambda}{\mu_U + \beta B}, \quad M_I = \frac{\Lambda \beta B}{(\sigma + \mu_1)(\mu_U + \beta B)}, \] (7)
where \( B \) is a positive root of the following equation:
\[ g(B) := a_0 B^2 + a_1 B + a_2 = 0, \] (8)
in which
\[ a_0 = \frac{v \beta}{K}, \quad a_1 = \frac{v \mu_U}{K} + \beta (\mu_B - v), \quad a_2 = (1 - R_0) [(\theta \beta + \delta) \Lambda + \mu_B \mu_U]. \] (9)

Set \( \Delta_0 = a_1^2 - 4a_0a_2 \). Then the potential positive roots of equation (8) are
\[ B^{1b} = \frac{K (-a_1 + \sqrt{\Delta_0})}{2v \beta}, \quad B^{2b} = \frac{K (-a_1 - \sqrt{\Delta_0})}{2v \beta}. \] (10)

Set
\[ M_U^{kb} = \frac{\Lambda}{\mu_U + \beta B^{kb}}, \quad M_I^{kb} = \frac{\Lambda \beta B^{kb}}{(\sigma + \mu_1)(\mu_U + \beta B^{kb})}, \quad k = 1, 2. \] (11)

Then, the existence of immune-free equilibria can be classified into four cases:
- System (2) has a unique immune-free equilibrium \( E_{1b}(M_U^{1b}, M_I^{1b}, B^{1b}, 0) \) if \( a_2 < 0 \);
- System (2) has no immune-free equilibrium if \( a_1 \geq 0 \) and \( a_2 \geq 0 \);
- System (2) has a unique immune-free equilibrium \( E_{1b}(M_U^{1b}, M_I^{1b}, B^{1b}, 0) \) if \( a_1 < 0 \) and \( a_2 = 0 \) or \( \Delta_0 = 0 \);
- System (2) has two immune-free equilibria \( E_{1b}(M_U^{1b}, M_I^{1b}, B^{1b}, 0) \) and \( E_{2b}(M_U^{2b}, M_I^{2b}, B^{2b}, 0) \) if \( a_1 < 0, a_2 > 0 \) and \( \Delta_0 > 0 \).

Note that \( \Delta_0 > 0 \) is equivalent to
\[ R_0 > 1 - \frac{[v \mu_U + K \beta (\mu_B - v)]^2}{4K v \beta [(\theta \beta + \delta) \Lambda + \mu_B \mu_U]} := R_0^*. \] (12)

Summarizing the discussions above, we have the following theorem.

**Theorem 2.2.** For the immune-free equilibria of system (2), the following statements are valid:
(i) If $R_0 > 1$, system (2) has a unique immune-free equilibrium $E_{1b}$.

(ii) If $K\beta(v - \mu_B) - v\mu_U > 0$ and $R_0 = 1$ or $R_0 > R_0^*$, system (2) has a unique immune-free equilibrium $E_{1b}$.

(iii) If $K\beta(v - \mu_B) - v\mu_U > 0$ and $R_0^* < R_0 < 1$, system (2) has two immune-free equilibria $E_{1b}$ and $E_{2b}$.

(iv) System (2) has no immune-free equilibrium otherwise.

Using the survival function method [12], we get the basic reproduction numbers of T cells:

$$R_k = \frac{\rho M^{kb}_1}{\mu_T}, \ k = 1, 2.$$  \hspace{1cm} (13)

Obviously, $R_1 \geq R_2$. Then we state the following theorem.

**Theorem 2.3.** For the stability of immune-free equilibrium of system (2), the following statements are valid:

1. Suppose $R_0 > 1$. Then $E_{1b}$ is locally asymptotically stable if $R_1 < 1$ and is unstable if $R_1 > 1$.

2. Suppose $K\beta(v - \mu_B) - v\mu_U > 0$ and $R_0^* < R_0 < 1$. Then $E_{2b}$ is unstable, and $E_{1b}$ is locally asymptotically stable if $R_1 < 1$ and is unstable if $R_1 > 1$.

**Proof.** Suppose $K\beta(v - \mu_B) - v\mu_U > 0$ and $R_0^* < R_0 < 1$. Then evaluating the Jacobian matrix at immune-free equilibrium $E_{kb} (k = 1, 2)$, we obtain

$$J(E_{kb}) = 
\begin{pmatrix}
-\mu_U - \beta B^{kb} & 0 & -\beta M^{kb}_U & 0 \\
\beta B^{kb} & -\left(\sigma + \mu_I\right) & \beta M^{kb}_U & 0 \\
-(\theta\beta + \delta)B^{kb} & N\sigma & -(\theta\beta + \delta)M^{kb}_U - \mu_B & 0 \\
0 & (\mu_U + \beta B^{kb}) & 0 & \rho M^{kb}_I - \mu_T \\
\end{pmatrix}.$$

Its characteristic equation is

$$(\lambda + \mu_T - \rho M^{kb}_I) \left(\lambda^3 + a_1 \left(B^{kb}\right) \lambda^2 + a_2 \left(B^{kb}\right) \lambda + a_3 \left(B^{kb}\right)\right) = 0,$$  \hspace{1cm} (14)

where

$$a_1(B^{kb}) = \mu_U + \beta B^{kb} + \sigma + \mu_I + \frac{vB^{kb}}{K} + N\sigma \frac{M^{kb}_I}{B^{kb}} > 0,$$

$$a_2(B^{kb}) = (\mu_U + \beta B^{kb})(\sigma + \mu_I) + \mu_U N\sigma \frac{M^{kb}_I}{B^{kb}} + a_3(B^{kb}) + (\sigma + \mu_I) \frac{vB^{kb}}{K},$$  \hspace{1cm} (15)

$$a_3(B^{kb}) = (\sigma + \mu_I) \left[\frac{vB^{kb}}{K} (\mu_U + \beta B^{kb}) + \beta \left(N\sigma M^{kb}_I - (\theta\beta + \delta)M^{kb}_U B^{kb}\right)\right].$$

It is easy to get that $\rho M^{kb}_I - \mu_T$ is a positive eigenvalue of $J(E_{1b})$ if and only if $R_1 > 1$. Therefore, $E_{1b}$ is unstable if $R_1 > 1$. For $R_1 < 1$, substituting (10) into (15), we obtain

$$a_3 \left(B^{1b}\right) > 0, \ a_2 \left(B^{1b}\right) > 0, \ a_1 \left(B^{1b}\right) a_2 \left(B^{1b}\right) - a_3 \left(B^{1b}\right) > 0.$$  \hspace{1cm} Using the Routh-Hurwitz criteria, all eigenvalues of $J(E_{1b})$ have negative real parts if $R_1 < 1$, which means $E_{1b}$ is locally asymptotically stable. Similarly, we get

$$a_3 \left(B^{2b}\right) = -(\sigma + \mu_I) B^{2b} \sqrt{\Delta_0} < 0.$$  \hspace{1cm} Hence $E_{2b}$ is unstable. The results for $R_0 > 1$ can be proved in a similar way. \hspace{1cm} $\Box$
In Theorem 2.2, we find that there exist two boundary equilibria, which indicates that the system (2) may undergo a backward bifurcation. Set

\[ a = \frac{(\sigma + \mu_I)^2 (K\beta(v - \mu_B) - v\mu_U)}{2K(\mu_U(\sigma + \mu_I)^2 + N\sigma\beta\Lambda)}. \]  

Then we obtain the following theorem by using the method shown in [3].

**Theorem 2.4.** For the bifurcations near the boundary equilibria, the following statements are valid:

1. System (2) undergoes a backward bifurcation at \( E_0 \) when \( R_0 \) crosses unity if \( a > 0 \) and a forward bifurcation if \( a < 0 \).
2. If \( R_1 > 1 \), system (2) undergoes a saddle-node bifurcation at immune-free equilibrium \( E_{1b} \) when \( R_0 \) crosses \( R^*_0 \).

The proof is shown in Appendix A.

3. **Analysis of positive equilibria.** In this section, we explore the existence of positive equilibria and consider the bifurcations from the positive equilibria.

3.1. **Existence of positive equilibria.** A positive equilibrium \( E(M_U, M_I, B, T) \) of system (2) satisfies:

\[
\begin{align*}
\Lambda - \mu_U M_U - \beta M_U B &= 0, \\
\beta M_U B - (\sigma + \mu_I) M_I - \alpha T M_I &= 0, \\
N\sigma M_I + v B \left(1 - \frac{B}{K}\right) - (\theta\beta + \delta) M_U B - \mu B B &= 0, \\
\rho M_I - \mu T &= 0.
\end{align*}
\]  

It follows that

\[
\begin{align*}
M_U &= \frac{\Lambda}{\mu_U + \beta B}, \\
M_I &= \frac{\mu_I}{\rho}, \\
T &= \frac{(\rho\Lambda - (\sigma + \mu_I)\mu_T)\beta B - (\sigma + \mu_I)\mu_T \mu_U}{\alpha \mu_I (\mu_U + \beta B)}.
\end{align*}
\]  

By substituting these expressions into (17), we get the following equation of \( B \)

\[ F_1(B) := c_1 B^3 + c_2 B^2 + c_3 B + c_4 = 0, \]  

where

\[
\begin{align*}
c_1 &= v\beta, \\
c_2 &= -(K\beta(v - \mu_B) - v\mu_U), \\
c_3 &= -\frac{K N\sigma \mu_U \mu_T}{\rho}, \\
c_4 &= K \left((\theta\beta + \delta)\Lambda + (\mu_B - v)\mu_U - \frac{N\sigma\beta\mu_T}{\rho}\right).
\end{align*}
\]  

Note that if \( \rho < (\sigma + \mu_I)\mu_T/\Lambda \), we have \( T < 0 \) for any \( B > 0 \), which means that there is no positive equilibrium. Thus, we assume \( \rho > (\sigma + \mu_I)\mu_T/\Lambda \) in the rest of this subsection and introduce the following symbols:

\[
\begin{align*}
P_1 &= c_2^2 - 3c_1 c_3, \\
Q_1 &= c_2 c_3 - 9c_1 c_4, \\
M_1 &= c_3^2 - 3c_2 c_4,
\end{align*}
\]  

and

\[
\begin{align*}
B_{11} &= \frac{-c_2 + \sqrt{P_1}}{3c_1}, \\
B_{12} &= \frac{-c_2 - \sqrt{P_1}}{3c_1}.
\end{align*}
\]  

\( B_{11}, B_{12} \) are the minimum and maximum of \( F_1(B) \) when \( P_1 > 0 \). According to [21], the discriminant of (19) is

\[ \Delta_1 := Q_1^2 - 4P_1 M_1. \]
A concrete analysis is given in Appendix B and results for the existence of the positive equilibria of system (2) are shown in Table 1.

### Table 1. Distribution of the positive equilibria

| Range of $R_0, R_1$ | Other conditions | Equilibria of system (2) |
|---------------------|------------------|--------------------------|
| $R_0 < R_0^*$       |                  | No positive equilibrium  |
| $R_0 > 1, R_1 < 1$  |                  | No positive equilibrium  |
| $R_0 > 1, R_1 > 1$  | $c_2 \geq 0$     | One positive equilibrium |
| $R_0 \geq 1, R_1 > 1$ | $c_2 < 0, c_3 < 0, \Delta_1 > 0$ | One positive equilibrium |
| $R_0 \geq 1, R_1 > 1$ | $c_2 < 0, c_3 > 0, \Delta_1 > 0$ | One positive equilibrium |
| $R_0 \geq 1, R_1 > 1$ | $c_2 < 0, c_3 > 0, P_1 < 0, \Delta_1 = 0$ | One positive equilibrium |
| $R_0 \geq 1, R_1 > 1$ | $c_2 < 0, c_3 > 0, P_1 > 0, \Delta_1 = 0$ | Two positive equilibria |
| $R_0 \geq 1, R_1 > 1$ | $c_2 < 0, c_3 > 0, \Delta_1 < 0$ | Three positive equilibria |
| $R_0 \geq 1, R_1 > 1$ | $c_2 < 0, R_0 = R_0^*$, $R_1 > 1$ | No positive equilibrium |
| $R_0' < R_0 < 1, R_2 > 1 > R_2$ | $c_2 < 0, P_1 > 0, \Delta_1 > 0$ | One positive equilibrium |
| $R_0' < R_0 < 1, R_2 > 1 > R_2$ | $c_2 < 0, P_1 > 0, \Delta_1 = 0$ | One positive equilibrium |
| $R_0' < R_0 < 1, R_2 > 1 > R_2$ | $c_2 < 0, P_1 > 0, \Delta_1 < 0, B_{11} > B_{12} > B_{21}$ | One positive equilibrium |
| $R_0' < R_0 < 1, R_2 > 1 > R_2$ | $c_2 < 0, P_1 > 0, \Delta_1 < 0, B_{21} < B_{12} < B_{11}$ | One positive equilibrium |
| $R_0' < R_0 < 1, R_2 > 1$ | $c_2 < 0, P_1 > 0, \Delta_1 = 0, B_{21} < B_{11} < B_{12}$ | Two positive equilibria |
| $R_0' < R_0 < 1, R_2 > 1$ | $c_2 < 0, P_1 > 0, \Delta_1 < 0, B_{21} < B_{11} < B_{12}$ | Two positive equilibria |

1. Two positive equilibria means that there are a simple equilibrium and a equilibrium of multiplicity 2. One positive equilibrium means that there is a equilibrium of multiplicity 2. One positive equilibrium means that system has a equilibrium of multiplicity 3.

### 3.2. Bifurcation analysis for positive equilibria

Assume $\bar{E}(M_U, M_I, \bar{B}, \bar{T})$ is a positive equilibrium of system (2). Then the Jacobian matrix of system (2) at $\bar{E}$ is

$$J(\bar{E}) = \begin{pmatrix} -\mu_U - B\bar{B} & 0 & -\beta M_U & 0 \\ \beta B \bar{B} & -(\sigma + \mu_I + \alpha \bar{T}) & -\beta M_U & -\alpha M_I \\ -N\sigma & v (1 - \frac{2B}{K}) & v (\frac{2B}{K} - 1) & -\alpha M_I \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$  

The characteristic equation of $J(\bar{E})$ is

$$\lambda^4 + b_1(\bar{B})\lambda^3 + b_2(\bar{B})\lambda^2 + b_3(\bar{B})\lambda + b_4(\bar{B}) = 0.$$  

where

$$b_1(\bar{B}) = \mu_U + \beta B + \mu_I + \sigma + \alpha \bar{T} + v \left(\frac{2B}{K} - 1\right) + (\theta \beta + \delta) M_U + \mu_B,$$

$$b_2(\bar{B}) = \alpha \rho \bar{T} M_I \left[ (\mu_U + \beta B) \left( v \left(\frac{2B}{K} - 1\right) + \mu_B \right) + \mu_U (\theta \beta + \delta) M_U \right],$$

$$b_3(\bar{B}) = \alpha \rho \bar{T} M_I \left[ -N \sigma \beta M_U + M_U (\theta \beta + \delta) (\mu_U + \mu_I + \sigma + \alpha \bar{T}) \right] + \left( v \left(\frac{2B}{K} - 1\right) + \mu_B \right) \left( \mu_U + \beta B + \mu_I + \sigma + \alpha \bar{T} \right)$$

and

$$b_4(\bar{B}) = -\beta M_U - \alpha M_I.$$
As shown in Theorem 3.1, system (2) undergoes a saddle-node bifurcation at \( \hat{E} \) topologically equivalent to \( \hat{E} \). Then \( \hat{E} \) is a Bogdanov-Takens point of codimension 2 and system (2) localized at \( \hat{E} \) is topologically equivalent to

\[
\begin{align*}
\dot{\Gamma}_1 &= \Gamma_2, \\
\dot{\Gamma}_2 &= \text{sgn}(F''(\hat{\theta}))\Gamma_2^3 + \text{sgn}(\Delta_2'(\hat{\theta}))\Gamma_1\Gamma_2 + O(|\Gamma_1, \Gamma_2|^3).
\end{align*}
\]

Thus, the matrix \( J(\hat{E}) \) has a zero eigenvalue if and only if \( b_4(\hat{B}) = 0 \). If \( b_4(\hat{B}) \neq 0 \), 0 is a simple eigenvalue. Using the method in [21], we can get the following theorem.

**Theorem 3.1.** Suppose \( \Delta_1 = 0 \). Then system (2) has a positive equilibrium \( \hat{E}(\hat{M}_U, \hat{M}_I, \hat{B}, \hat{T}) \) of multiplicity 2 if one of the following conditions is satisfied:

\( (A_1) \) \( e_2 < 0, e_3 > 0, P_1 > 0, R_0 \geq 1 \) and \( R_1 > 1 \);

\( (A_2) \) \( e_2 < 0, P_1 > 0, B^{2b} < B_{12}, R_0' < R_0 < 1 \) and \( R_1 > 1 > R_2 \);

\( (A_3) \) \( e_2 < 0, P_1 > 0, B^{2b} < B_{12}, R_0' < R_0 < 1 \) and \( R_2 = 1 \);

\( (A_4) \) \( e_2 < 0, P_1 > 0, R_0' < R_0 < 1, B^{2b} < B_{11} \) and \( R_2 > 1 \).

Moreover, system (2) undergoes a saddle-node bifurcation at \( \hat{E} \) if \( b_3(\hat{B}) \neq 0 \).

For the positive equilibrium \( \hat{E} \), we let

\[
\Delta_2 = -b_1(\hat{B})^2 b_4(\hat{B}) + b_1(\hat{B}) b_2(\hat{B}) b_3(\hat{B}) - b_3(\hat{B})^2.
\]

Using the method shown in [28], we get the following theorem.

**Theorem 3.2.** The Hopf bifurcation of system (2) occurs at \( \hat{E} \) if and only if \( \Delta_2 = 0 \), \( b_4(\hat{B}) \neq 0 \) and \( b_3(\hat{B}) > 0 \).

Suppose \( \Delta_1 = 0 \) and one of the conditions \( (A_1), (A_2), (A_3) \) and \( (A_4) \) in Theorem 3.1 are satisfied. Then system (2) has a positive equilibrium \( \hat{E}(\hat{M}_U, \hat{M}_I, \hat{B}, \hat{T}) \) of multiplicity 2, where

\[
\begin{align*}
\hat{M}_U &= \frac{2P_1 A}{2P_1 \mu_U - \beta Q_1}, \quad \hat{M}_I = \frac{\mu_T}{\rho}, \quad \hat{B} = -\frac{Q_1}{2P_1}, \\
\hat{T} &= -\frac{\rho \beta \Delta Q_1 + \mu_T (\sigma + \mu_I)(2P_1 \mu_U - \beta Q_1)}{2\alpha \mu_T P_1 \mu_U - \beta Q_1}.
\end{align*}
\]

As shown in Theorem 3.1, system (2) undergoes a saddle-node bifurcation at \( \hat{E} \) if \( b_3(\hat{B}) \neq 0 \). If \( b_3(\hat{B}) = 0 \), the Jacobian matrix \( J(\hat{E}) \) has double zero eigenvalues. We prove below that \( \hat{E} \) is a Bogdanov-Takens point.

**Theorem 3.3.** Assume one of the conditions \( (A_1), (A_2), (A_3) \) and \( (A_4) \) shown in Theorem 3.1 is satisfied. Suppose

\[
\Delta_1 = 0, \quad b_3(\hat{B}) = 0, \quad F''(\hat{\theta}) \neq 0 \text{ and } \Delta_2'(\hat{\theta}) \neq 0.
\]

Then \( \hat{E} \) is a Bogdanov-Takens point of codimension 2 and system (2) localized at \( \hat{E} \) is topologically equivalent to

\[
\begin{align*}
\dot{\Gamma}_1 &= \Gamma_2, \\
\dot{\Gamma}_2 &= \text{sgn}(F''(\hat{\theta}))\Gamma_2^3 + \text{sgn}(\Delta_2'(\hat{\theta}))\Gamma_1\Gamma_2 + O(|\Gamma_1, \Gamma_2|^3).
\end{align*}
\]
Proof. Firstly, let \( x = M_U - \dot{M}_U, y = M_I - \dot{M}_I, z = B - \dot{B}, w = T - \dot{T} \). Then the equilibrium \( \bar{E} \) is brought to the origin and system (2) becomes

\[
\begin{align*}
\frac{dx}{dt} &= -\mu_U x - \beta \dot{B} x - \beta \dot{M}_U z - \beta xz, \\
\frac{dy}{dt} &= \beta \dot{B} x - \beta \dot{M}_U z + \beta xz - (\sigma + \mu_I) y - \alpha \dot{T} y - \alpha \dot{M}_I w - \alpha yw, \\
\frac{dz}{dt} &= N \sigma y + v z \left( 1 - \frac{z + 2 \dot{B}}{K} \right) - (\theta \beta + \delta) (\dot{B} x + \dot{M}_U z + xz) - \mu_B z, \\
\frac{dw}{dt} &= \rho \dot{T} y + \rho yw.
\end{align*}
\]

After calculation, we obtain that the Jacobian matrix \( J(\bar{E}) \) has four eigenvalues: \( \lambda_1 = \lambda_2 = 0 \) and

\[
\lambda_3 = \frac{-b_1(\dot{B}) + \sqrt{\Delta_3}}{2}, \quad \lambda_4 = \frac{-b_1(\dot{B}) - \sqrt{\Delta_3}}{2},
\]

where \( \Delta_3 = b_1^2(\dot{B}) - 4b_2(\dot{B}) \), and \( b_1(\dot{B}), b_2(\dot{B}) \) are shown in (25).

Furthermore, we can prove that if \( \Delta_1 = b_3(\dot{B}) = 0 \),

\[
b_1(\dot{B}) > 0, \quad b_2(\dot{B}) > 0, \quad \Delta_3 > 0.
\]

Thus \( \lambda_4 < \lambda_3 < 0 \). The generalized eigenvectors corresponding to 0 are

\[
V_1 = \left( -\frac{\Lambda \beta}{\left( \mu_U + \beta \dot{B} \right)^2}, 0, 1, \frac{\rho \mu_U \Lambda \beta}{\alpha \mu_T \left( \mu_U + \beta \dot{B} \right)^2} \right),
\]

\[
V_2 = \left( \frac{\Lambda \beta}{\left( \mu_U + \beta \dot{B} \right)^2}, \frac{\left( \mu_U + \beta \dot{B} \right)^3 + (\theta \beta + \delta) \Lambda \beta \dot{B}}{N \sigma \left( \mu_U + \beta \dot{B} \right)^3}, 0, -\frac{\rho \Lambda \beta \mu_U}{\alpha \mu_T \left( \mu_U + \beta \dot{B} \right)^3} \right),
\]

\[
\sqrt{\frac{\rho^2 \Lambda \beta \dot{B}}{\alpha K \mu_U^2 N \sigma \left( \mu_U + \beta \dot{B} \right)^2}}.
\]

And the corresponding eigenvectors of \( \lambda_3, \lambda_4 \) are

\[
V_3 = \left( 1, V_{32}, V_{33}, \frac{N \sigma p V_{32} \left( \rho \beta J - \mu_T (\sigma + \mu_I) (\mu_U + \beta \dot{B}) \right)}{\alpha \mu_T N \sigma \Lambda \beta \mu_U (\mu_U + \beta \dot{B})} \right),
\]

\[
V_4 = \left( 1, V_{42}, V_{43}, \frac{N \sigma p V_{42} \left( \rho \beta J - \mu_T (\sigma + \mu_I) (\mu_U + \beta \dot{B}) \right)}{\alpha \mu_T N \sigma \Lambda \beta \mu_U (\mu_U + \beta \dot{B})} \right),
\]

where

\[
V_{32} = \frac{(\theta \beta + \delta) \dot{B} + V_{33} \dot{V}_{32}}{N \sigma}, \quad V_{42} = \frac{(\theta \beta + \delta) \dot{B} + V_{43} \dot{V}_{42}}{N \sigma},
\]

\[
V_{33} = \frac{-\left( \mu_U + \beta \dot{B} \right) \left( \mu_U + \beta \dot{B} + \dot{\lambda}_3 \right)}{\Lambda \beta}, \quad \dot{V}_{32} = \frac{N \sigma \dot{M}_I}{\dot{B}} + \frac{\dot{V}_{33}}{K}, \quad \dot{\lambda}_3,
\]

\[
V_{43} = \frac{-\left( \mu_U + \beta \dot{B} \right) \left( \mu_U + \beta \dot{B} + \dot{\lambda}_4 \right)}{\Lambda \beta}, \quad \dot{V}_{42} = \frac{N \sigma \dot{M}_I}{\dot{B}} + \frac{\dot{V}_{43}}{K}, \quad \dot{\lambda}_4.
\]
By using the near-identity transformation

\[
L = [V_1, V_2, V_3, V_4] \quad \text{and} \quad \begin{pmatrix} x \\ y \\ z \\ w \end{pmatrix} = L \begin{pmatrix} \Gamma_1 \\ \Gamma_2 \\ \Gamma_3 \\ \Gamma_4 \end{pmatrix}.
\]

(32)

Then system (29) becomes

\[
\begin{aligned}
\dot{\Gamma}_1 &= \Gamma_2 + L_{20} \Gamma_1^2 + L_{11} \Gamma_1 \Gamma_2 + L_{02} \Gamma_2^2 + \sum_{i=1,2,3,4} m_i \Gamma_i \Gamma_3 + \sum_{j=1,2,4} n_j \Gamma_4 \Gamma_j, \\
\dot{\Gamma}_2 &= M_{02} \Gamma_1^2 + M_{11} \Gamma_1 \Gamma_2 + M_{02} \Gamma_2^2 + \sum_{i=1,2,3,4} \tilde{m}_i \Gamma_i \Gamma_3 + \sum_{j=1,2,4} \tilde{n}_j \Gamma_4 \Gamma_j, \\
\dot{\Gamma}_3 &= \lambda_3 \Gamma_3 + \mathcal{O}(|\Gamma_1, \Gamma_2, \Gamma_3, \Gamma_4|^2), \\
\dot{\Gamma}_4 &= \lambda_4 \Gamma_4 + \mathcal{O}(|\Gamma_1, \Gamma_2, \Gamma_3, \Gamma_4|^2).
\end{aligned}
\]

(33)

For \( \Gamma_1, \Gamma_2 \to 0 \), there exists a center manifold

\[ C := \{(\Gamma_3, \Gamma_4) | \Gamma_3 = h_1(\Gamma_1, \Gamma_2), \Gamma_4 = h_2(\Gamma_1, \Gamma_2) \}. \]

Restricting system (33) on this center manifold, we have

\[
\begin{aligned}
\dot{\Gamma}_1 &= \Gamma_2 + L_{20} \Gamma_1^2 + L_{11} \Gamma_1 \Gamma_2 + L_{02} \Gamma_2^2 + \mathcal{O}(|\Gamma_1, \Gamma_2|^3), \\
\dot{\Gamma}_2 &= M_{02} \Gamma_1^2 + M_{11} \Gamma_1 \Gamma_2 + M_{02} \Gamma_2^2 + \mathcal{O}(|\Gamma_1, \Gamma_2|^3).
\end{aligned}
\]

(34)

By using the near-identity transformation

\[
\begin{aligned}
\Gamma_1 &= X + \frac{1}{2} (L_{11} + M_{02}) X^2 + L_{02} X Y + \mathcal{O}(|X, Y|^3), \\
\Gamma_2 &= Y - L_{20} X^2 + M_{02} X Y + \mathcal{O}(|X, Y|^3),
\end{aligned}
\]

(35)

and rewriting \( X, Y \) as \( \Gamma_1, \Gamma_2 \), we get

\[
\begin{aligned}
\dot{\Gamma}_1 &= \Gamma_2, \\
\dot{\Gamma}_2 &= M_{20} \Gamma_1^2 + (M_{11} + 2L_{20}) \Gamma_1 \Gamma_2 + \mathcal{O}(|\Gamma_1, \Gamma_2|^3).
\end{aligned}
\]

(36)

It is proved in Appendix C that

\[
\text{sgn}(M_{20}) = -\text{sgn}(F''(\hat{B})), \quad \text{sgn}(M_{11} + 2L_{20}) = -\text{sgn}(\Delta_2'(\hat{B})).
\]

(37)

Since \( F''(\hat{B}) \neq 0 \) and \( \Delta_2'(\hat{B}) \neq 0 \), through rescaling the time and variables as

\[
(\Gamma_1, \Gamma_2, t) \to \left( -\frac{M_{20}}{(M_{11} + 2L_{20})^2} \Gamma_1, -\frac{M_{20}^2}{(M_{11} + 2L_{20})^3} \Gamma_2, \frac{(M_{11} + 2L_{20})}{M_{20}} \right),
\]

system (36) is topologically equivalent to system (28). \( \square \)

In Theorem 3.3, the Bogdanov-Takens bifurcation is a bifurcation of codimension 2 if \( F''(\hat{B}) \Delta_2'(\hat{B}) \neq 0 \). Now we show that this Bogdanov-Takens bifurcation will be degenerate if \( F''(\hat{B}) = 0 \).

**Theorem 3.4.** Suppose that the equilibrium \( \hat{E}(\hat{M}_u, \hat{M}_l, \hat{B}, \hat{T}) \) satisfies the following equations

\[
F(\hat{B}) = F'(\hat{B}) = F''(\hat{B}) = 0, \quad b_3(\hat{B}) = 0.
\]

Then \( \hat{E} \) is a nilpotent focus/elliptic point.
Proof. Using the linear transformation shown in (32), the system (2) becomes (33). In this case we need to study the system (33) up to $O(|\Gamma_1,\Gamma_2|^4)$. Firstly, by direct calculations we see that the center manifold has the following form

$$\Gamma_3 = h_1(\Gamma_1, \Gamma_2) = \sum_{i,j \in \mathbb{N}} a_{ij} \Gamma_1^i \Gamma_2^j + O(|\Gamma_1,\Gamma_2|^4),$$

$$\Gamma_4 = h_2(\Gamma_1, \Gamma_2) = \sum_{i,j \in \mathbb{N}} b_{ij} \Gamma_1^i \Gamma_2^j + O(|\Gamma_1,\Gamma_2|^4).$$

By reducing the system onto this center manifold, we obtain

$$\begin{align*}
\dot{\Gamma}_1 &= \Gamma_2 + \sum_{2 \leq i+j \leq 4} L_{ij} \Gamma_1^i \Gamma_2^j + O(|\Gamma_1,\Gamma_2|^5), \\
\dot{\Gamma}_2 &= \sum_{2 \leq i+j \leq 4} M_{ij} \Gamma_1^i \Gamma_2^j + O(|\Gamma_1,\Gamma_2|^5) .
\end{align*}$$

(39)

Next, to eliminate the $\Gamma_2^2$ terms in system (39), we make the following near-identity transformation

$$\begin{align*}
\overset{\sim}{\Gamma}_1 &= X + \frac{1}{2} (L_{11} + M_{02}) X^2 + L_{02} XY, \\
\overset{\sim}{\Gamma}_2 &= Y - L_{20} X^2 + M_{02} XY.
\end{align*}$$

(40)

Rewriting $X, Y$ as $\Gamma_1, \Gamma_2$, system (39) becomes

$$\begin{align*}
\overset{\sim}{\dot{\Gamma}}_1 &= \Gamma_2 + \sum_{3 \leq i+j \leq 4} a_{ij} \Gamma_1^i \Gamma_2^j + O(|\Gamma_1,\Gamma_2|^5), \\
\overset{\sim}{\dot{\Gamma}}_2 &= b_{11} \Gamma_1 \Gamma_2 + b_{30} \Gamma_1^3 + b_{21} \Gamma_1^2 \Gamma_2 + b_{12} \Gamma_1 \Gamma_2^2 + \sum_{i+j=4} b_{ij} \Gamma_1^i \Gamma_2^j + O(|\Gamma_1,\Gamma_2|^5) ,
\end{align*}$$

(41)

where

$$b_{11} = M_{11} + 2L_{20}, \quad b_{30} = M_{30} - M_{11}L_{20}.$$

(42)

It is proved in Appendix D that

$$b_{11} < 0, \quad b_{30} < 0.$$

(43)

Using Lemma 3.1 in [2], system (2) localized at $\overset{\sim}{E}$ is topologically equivalent to

$$\begin{align*}
\overset{\sim}{\dot{\Gamma}}_1 &= \overset{\sim}{\Gamma}_2, \\
\overset{\sim}{\dot{\Gamma}}_2 &= (M_{11} + 2L_{20}) \overset{\sim}{\Gamma}_1 \overset{\sim}{\Gamma}_2 + (M_{30} - M_{11}L_{20}) \overset{\sim}{\Gamma}_1^3 + (b_{21} + 3a_{30}) \overset{\sim}{\Gamma}_1^2 \overset{\sim}{\Gamma}_2 \\
&+ (b_{40} - b_{11}a_{30}) \overset{\sim}{\Gamma}_1^4 + \left(4a_{40} + b_{31} + \frac{1}{3}b_{11}b_{12}\right) \overset{\sim}{\Gamma}_1^3 \overset{\sim}{\Gamma}_2 + O(|\Gamma_1,\Gamma_2|^5),
\end{align*}$$

(44)

where $a_{30}, b_{21}$ and $b_{40}$ are shown in Appendix E. $a_{40}, b_{12}, b_{31}$ and $b_{31}$ are complex and not presented here.

Set

$$\Phi(\mu_T) := 5b_{30}(b_{21} + 3a_{30}) - 3b_{11}(b_{40} - b_{11}a_{30}),$$

$$Q(\mu_T) := b_{11}^2 + 8b_{30}.$$

(45)
After simplifications, we obtain
\[ Q(\mu_T) = \frac{-24v^2\beta S_{30}(\mu_T - \mu_{T1})(\mu_T - \mu_{T2})}{S_{21}^2(K\beta(v - \mu_B) - v\mu_U)^2}, \]  
where
\[ \mu_{T1} = \frac{-S_{31} + \sqrt{\Delta_3}}{2S_{30}}, \quad \mu_{T2} = \frac{-S_{31} - \sqrt{\Delta_3}}{2S_{30}}, \]
\[ S_{30} = -\frac{3}{8}v^2(K\beta(v - \mu_B) + 2v\mu_U)^2(K\beta(3\mu_U + v - \mu_B) - v\mu_U)^4, \]
\[ S_{31} = \frac{3}{2}\mu_U(3\beta + \frac{v}{2})(K\beta(v - \mu_B) - v\mu_U)^3(K\beta(v - \mu_B) + 2v\mu_U) \]
\[ J = (K\beta(3\mu_U + v - \mu_B) - v\mu_U)^4(K\beta(v - \mu_B) - v\mu_U)^2 \]
\[ \Delta_3 = \frac{3}{2}S_{31}\mu_U^2(K\beta(3\mu_U + v - \mu_B) - v\mu_U)^2(K\beta(v - \mu_B) - v\mu_U)^2 \]
\[ \Delta_3 < 0, \]
and \( S_{21} \) is shown in (D.63). It is easy to know that \( \mu_{T1} > 0, \mu_{T2} < 0 \).

Let
\[ \mu_{T1}^* = \frac{\mu_U(K\beta(v - \mu_B) - v\mu_U)^2}{(K\beta(3\mu_U + v - \mu_B) - v\mu_U)((K\beta(v - \mu_B) + 2v\mu_U) - 1)}, \]
\[ \mu_{T2}^* = \frac{\mu_U(K\beta(v - \mu_B) - v\mu_U)^2}{(K\beta(3\mu_U + v - \mu_B) - v\mu_U)((K\beta(v - \mu_B) + 2v\mu_U)}. \]

Then, it can be seen in Appendix D that \( \mu_T \in (\max(\mu_{T1}^*, \mu_{T2}^*), +\infty) \) must be satisfied to ensure the positivity of \( T \) and other parameters.

Define \( J = (\max(\mu_{T1}^*, \mu_{T2}^*), +\infty) \) and
\[ J_1 = \{ \mu_T \in J | \mu_T \in (\max(\mu_{T1}^*, \mu_{T2}^*), \mu_{T1}) \}, \]
\[ J_2 = \{ \mu_T \in J | \mu_T \in (\mu_{T1}, +\infty) \}, \]
\[ J_3 = \{ \mu_T \in J | \mu_T = \mu_{T1} \}, \]
\[ J_4 = \{ \mu_T \in J | \mu_T = \Phi(\mu_T) \} \]

According to [2, 6, 21], we have
\[ J_1 \]
\[ J_2 \]
\[ J_3 \]
\[ J_4 \]

4. Numerical results. In this section, numerical simulations are carried out to explore richer dynamical behaviors of system (2). For the convenience of simulations, the parameters given in Table 2 are dimensioned. In Figure 1, we show that system (2) undergoes a backward or forward bifurcation.

Now we focus on the bifurcation that occurs near the positive equilibria. In the rest of this section, we fix \( \sigma = 0.4, \mu_T = 0.0005, v = 0.41, \mu_B = 0.05, \mu_T = 0.008, K = 7 \times 10^5, \beta = 1.1 \times 10^{-7}, \alpha = 2.9 \times 10^{-5}, \theta = 1.05, \delta = 3.26 \times 10^{-6} \) and \( \rho = 3.75 \times 10^{-5} \) in all simulations.

Based on Theorems 3.1, 3.2 and 3.3, we choose \( N \) and \( \mu_U \) as bifurcation parameters to obtain the bifurcation diagram of system (2) shown in Figure 2. The plane of \( (\mu_U, N) \) is divided into four regions by saddle-node curves shown by black and green lines. System (2) has three positive equilibria in region III, two positive
1.2

Figure 1. Backward and forward bifurcation. Blue (red) curves represent the stable (unstable) singularities and SN denotes saddle-node bifurcation. Parameters are taken as: \( \mu_U = 0.025 \), \( \beta = 1.1 \times 10^{-7} \), \( \alpha = 2.9 \times 10^{-5} \), \( K = 7 \times 10^5 \), \( \delta = 2.7 \times 10^{-6} \), \( \mu_T = 0.008 \), \( \rho = 4.9 \times 10^{-7} \), \( \Lambda = 5100 \). (a) \( v = 0.41 \), \( \mu_B = 0.05 \). (b) \( v = 0.15 \), \( \mu_B = 0.12 \).

Table 2. Parameter range and source for simulation.

| Para. | Range    | Units | Source | Para. | Range    | Units | Source |
|-------|----------|-------|--------|-------|----------|-------|--------|
| \( \Lambda \) | 600 - 7000 | 1/ml day | [5, 13] | \( \mu_U \) | see text | 1/day |        |
| \( \sigma \) | 0.011 - 0.5 | 1/day | [5, 13] | \( \mu_I \) | 0 - 2 | 1/day | [5]    |
| \( \beta \) | 2.5 \times 10^{-11} - 10^{-5} | 1/day | [5, 13] | \( v \) | 0 - 0.52 | 1/day | [13]   |
| \( N \) | 0.05 - 100 | 1/day | [5, 13] | \( \mu_B \) | 0-0.52 | 1/day | [4, 13] |
| \( K \) | 10^7 - 10^{10} | 1/day | [5, 13] | \( \theta \) | 0.025 - 50 | 1/day | [5] |
| \( \delta \) | 10^{-9} - 10^{-6} | 1/ml day | [5] | \( \mu_T \) | 0.01 - 0.33 | 1/day | [5] |
| \( \rho \) | 10^{-8} - 1 | 1/day | [5] | \( \alpha \) | 2 \times 10^{-5} - 3 \times 10^{-5} | 1/day | [13] |

equilibria in region I, a unique positive equilibrium in region IV and no positive equilibrium in region II. The two black lines meet with each other at CP (Cusp bifurcation point). Furthermore, the Hopf bifurcation curve meets with saddle-node bifurcation curve at BT (Bogdanov-Takens bifurcation) and is divided by three DH (Degenerate Hopf bifurcation points) into four parts, where the red and blue lines stand for supercritical and subcritical Hopf bifurcation respectively.

Usually, much attentions have been paid to the relationship between the amount of Mtb and \( R_0 \) [5, 13, 29]. We obtain firstly the bifurcation diagram of positive equilibria in the plane \((R_0, B)\) shown in Figure 3, where blue (red) curve stands for stable (unstable) equilibrium and \( H^+ \) and \( H^- \) \((i = 1, 2, 3)\) represent subcritical Hopf bifurcation and supercritical Hopf bifurcation respectively. It is worth to note that the bifurcation curve of positive equilibria in Figure 3 (a) is an ‘S’ shape and it is divided by saddle-node bifurcation (SN) into three branches and we call the lower and upper branches as latency and active diseases. We see that both branches are locally stable as \( R_0^- < R_0 < R_0^+ \), which indicates that the disease may progress to latency or active disease depending on the initial amount of Mtb.
Figure 2. Bifurcation diagram of system (2). The black and green lines represent saddle-node bifurcation. The blue (red) line stands for subcritical (supercritical) Hopf bifurcation. CP, BT, and DH denote Cusp-bifurcation, Bogdanov-Takens bifurcation and Degenerate Hopf bifurcation respectively.

Figure 3. Bifurcation of positive equilibria. Blue (red) curve stands for stable (unstable) equilibrium. SN, $H^+$ and $H^-$ ($i = 1, 2, 3$) represent saddle-node bifurcation, subcritical Hopf bifurcation and supercritical Hopf bifurcation respectively. The positive equilibrium coalesce with the boundary equilibrium at BP point.

Note that the equilibrium in Figure 3 may lose its stability due to the Hopf bifurcation and a periodic solution is present. In the other hand, from Figure 2, we know that there exist Degenerate Hopf bifurcation and Bogdanov-Takens bifurcation in system (2), which means that multi-periodicity, homoclinic orbit and saddle-node of limit cycle may occur. To observe these behaviors, in Figure 4, we obtain the bifurcation including periodic solutions of system (2) in plane $(R_0, B)$.

In Figures 4 (a) and (b), the saddle-node of limit cycle ($SN_{lc}$) occurs at $R_0 = 2.93$ and $R_0 = 4.489$ respectively. In both cases, the unstable periodic solutions disappear at the subcritical Hopf bifurcation $H^+$. However, the reasons for the disappearance of the large periodic solutions in these two cases are different. Indeed, the disappearance of large periodic solution is due to homoclinic bifurcation $Hom$ at $R_0 = 3.664$ in Figure 4 (a) and large periodic solution disappears at the supercritical
Hopf bifurcation $H_2^-$ at $R_0 = 3.198$ in Figure 4 (b). In those bifurcation diagrams, we still call the lower and higher amount of Mtb as latency and active diseases respectively. An interesting phenomenon can be found on the lower branch of bifurcation diagram (latency disease) shown in Figure 4 (d), the steady state of Mtb is a stable periodic solution as the value of $R_0$ is less than the location of $H_1^-$ and becomes a stable equilibrium as the value of $R_0$ is larger than the location of $H_1^-$. 

![Image of bifurcation diagrams](image-url)

Figure 4. Bifurcation of positive equilibria with periodic solution involved. Blue (red) curve stands for stable (unstable) equilibrium or periodic solution. $SN_{lc}$, $H_i^+$ and $H_i^-$ ($i = 1, 2, 3$) represent saddle-node bifurcation of limit cycle, subcritical Hopf bifurcation and supercritical Hopf bifurcation respectively. (d) We magnify the small neighborhood of $H_1^-$ in (c).

5. Discussion and Conclusions. Exploring the causes for the differences between infection processes of Mtb is currently an open and highly concerned issue. In this paper, considering the acceleration effect of T cells on their own recruitment, the bilinear recruitment function of T cells is introduced into a four-dimensional model to describe the dynamics of Mtb in host. In Section 2, we study the boundary equilibria for system (2). Then we study the existence of positive equilibria of system (2) and pay attention to analyze the bifurcations near the positive equilibria in Section 3. We show that system (2) undergoes the saddle-node bifurcation, Hopf bifurcation and Bogdanov-Takens bifurcation of codimension 2 and 3 and obtain Theorems 3.1, 3.2, 3.3 and 3.4 respectively.

Unlike other studies [5, 13, 29], we have shown in Theorem 2.3 that there exists a stable immune-free equilibrium $E_{1b}$ with bacterial load when the reproduction
number of immune response $R_1$ is less than unity. That phenomenon means that the probability of developing active tuberculosis is greatly elevated for people with weak or deficient acquired immunity, as advocated by [7]. In addition, if the condition for the backward bifurcation is met and $R_1 > 1$, there may exist three positive equilibria and a stable periodic solution when the reproductive number of bacteria $R_0$ is less than unity (shown in Fig 3 (a)). These findings show that the incorporation of bilinear recruitment function of T cells leads to more complex dynamical behaviors of system, compared with [13]. Therefore, it is important to inhibit the intracellular growth or enhancing the sterilization of macrophages until $R_0 < 1$ so that Mtb can be eliminated.

Furthermore, the Bogdanov-Takens bifurcation of codimension 3 in system (2) induces richer dynamical behaviors such as the degenerate Hopf bifurcation, two limit cycles, saddle-node of limit cycle, a homoclinic loop, large-amplitude oscillations and small-amplitude oscillations. These phenomena are not observed in [5, 11, 13, 29]. It should be noted that as the parameters stay in the neighborhood of the $SN_{lc}$, there exist a stable periodic solution, an unstable periodic solution and a stable equilibrium. In particular, near the homoclinic bifurcation point, this stable periodic solution with large amplitude introduces slow-fast behavior in system (2) (see Figure 5 (b)), which suggests that latency can be a dynamic process that may rapidly progress to reactivation. On the other hand, a small oscillation appears in the neighborhood of Hopf bifurcation $H_{-1}$ and the time-series diagram is shown in Figure 5 (a) where Mtb is in low levels for a long time. A reasonable explanation is given for the slow reactivation of latent infection. These discoveries suggest that it is important in practice to design a therapy protocol according to disease status and personal parameters in system (2) such that the orbit of disease lies in the Mtb-control region.

In conclusion, considering the acceleration effect of T cells on their own recruitment makes the dynamics of in-host Mtb complicated. In this work, we focus on the interactions in granuloma. Notice that the mutual influence between granuloma and the total lung response plays an important role in Mtb infection and the scales of dynamics involved in the lung and granuloma are different [9, 17]. It is important to use mathematical models to capture effects occurring at different scales. We leave it as future research.
Appendix A. Proof of Theorem 2.4. (1) By using the technique of central manifold, we examine the case (1) of Theorem 2.4. Firstly, let $x_1 = M_U - \Lambda/\mu_U, x_2 = M_I, x_3 = B, x_4 = T$. Then system (2) becomes

\begin{align*}
\frac{dx_1}{dt} &= \mu_U x_1 - \beta(x_1 + \Lambda/\mu_U)B := f_1, \\
\frac{dx_2}{dt} &= \beta(x_1 + \Lambda/\mu_U)B - (\sigma + \mu_I)x_2 - \alpha x_2 x_4 := f_2, \\
\frac{dx_3}{dt} &= N \sigma x_2 + v x_3 \left(1 - \frac{x_3}{K}\right) - (\theta \beta + \delta)(x_1 + \Lambda/\mu_U)x_3 - \mu_B x_3 := f_3, \\
\frac{dx_4}{dt} &= \rho x_2 x_4 - \mu_T x_4 := f_4.
\end{align*}

(A.49)

It can be seen that $R_0 = 1$ corresponds to $N = N^* = ((\theta \beta + \delta)\Lambda + \mu_U(\mu_B - v))(\sigma + \mu_I)/(\Lambda \beta \sigma)$. The linearization matrix of system (A.49) at $(0, 0, 0, 0)$ with $R_0 = 1$ is

$$D_x f = J(E_0)|_{R_0=1},$$

where $J(E_0)$ is shown in (4). If $R_0 = 1$, 0 is a simple eigenvalue of $D_x f$, and all the other three eigenvalues have negative real parts. A right eigenvector associated with the 0 eigenvalue is

$$r = [-\Lambda \beta / \mu_U^2, \Lambda \beta / (\mu_U (\sigma + \mu_I)), 1, 0]' ,$$

and the left eigenvector satisfying $l \cdot r = 1$ is

\begin{align*}
l &= \left[0, \frac{\mu_U (\sigma + \mu_I)(\mu_U (\mu_B - v) + (\theta \beta + \delta)\Lambda)}{\Lambda \beta (\mu_U (\sigma + \mu_I) + \mu_U (\mu_B - v) + (\theta \beta + \delta)\Lambda)}, \frac{\mu_U (\sigma + \mu_I)}{\mu_U (\sigma + \mu_I) + \mu_B - v}, 0\right] .
\end{align*}

Then by direct calculations, we get

\begin{align*}
a &:= \sum_{i,j,h=1}^4 l_i r_j r_h \frac{\partial^2 f_i}{\partial x_j \partial x_h}(0, 0, 0, 0) \\
&= \frac{1}{2K \mu_U} (K \beta (v - \mu_B) - v \mu_U) l_3 \\
&= \frac{(\sigma + \mu_I)^2 (K \beta (v - \mu_B) - v \mu_U)}{2K(\mu_U (\sigma + \mu_I)^2 + N \sigma \beta \Lambda)} ,
\end{align*}

\begin{align*}
b &:= \sum_{i,j=1}^4 l_i r_j \frac{\partial^2 f_i}{\partial x_j \partial N}(0, 0, 0, 0) \\
&= \frac{\sigma \Lambda \beta}{\mu_U (\sigma + \mu_I)} l_3 \\
&= \frac{\Lambda \beta \sigma (\sigma + \mu_I)}{\mu_U (\sigma + \mu_I)^2 + N \sigma \beta \Lambda} > 0 .
\end{align*}

It follows from [3] that system (2) undergoes a backward bifurcation at $E_0$ if $a < 0$ and a forward bifurcation if $a > 0$.

(2) For $R_0 = R_0^*$, system (2) have an immune-free equilibrium $E_{1b}$ of multiplicity 2. As shown in the proof of Theorem 2.3, the characteristic equation is (14). For $R_1 > 1, R_0 = R_0^*$, we can get that the Jacobian matrix at $E_{1b}$ has a simple zero eigenvalue if and only if $R_0 = R_0^*$ and all the other eigenvalues have negative real parts. Moreover, we have $a_2(B^{1b}) > 0$, thus if $R_1 > 1$, system (2) undergoes a saddle-node bifurcation at $E_{1b}$ when $R_0$ crosses $R_0 = R_0^*$. 


Appendix B. Existence of positive equilibria for system (2). To ensure the positivity of $T$, we let

$$F_3(B) = KN\sigma \left( \frac{\Lambda}{\sigma + \mu_I} - \frac{\mu_T}{\rho} \right) \beta B - \frac{\mu_U \mu_T}{\rho} \right).$$

(B.50)

It is easy to know that $T > 0$ is equivalent to $F_3(B) > 0$. Set

$$\tilde{B} = \mu_U \mu_T (\sigma + \mu_I) / (\beta (\rho \Lambda - \mu_T (\sigma + \mu_I))).$$

Then $F_3(\tilde{B}) = 0$ and $\tilde{B} > 0$ if $\rho > \mu_T (\sigma + \mu_I) / \Lambda$.

Now we use the intersection of $F_1(B)$ and $F_3(B)$ to determine whether the roots of (19) satisfy $B > \tilde{B}$. It can be verified that

$$g(B) = \frac{F_1(B) - F_3(B)}{B},$$

where $g(B)$ is shown in (8). Hence, the existence of interaction of $F_1(B)$ and $F_3(B)$ in region $B > 0$ is equivalent to that of immune-free equilibria. Similar to Theorem 2.2, we study the existence of positive equilibria in three cases: $R_0 \geq 1, R_0^* \leq R_0 < 1$ and $R_0 < R_0^*$. After calculations, we get

$$F_1(0) = F_3(0), \quad F_1'(0) = c_3, \quad F_3'(0) = KN\sigma \beta \left( \frac{\Lambda}{\sigma + \mu_I} - \frac{\mu_T}{\rho} \right) > 0.$$

Obviously, $R_0 < 1$ is equivalent to $F_3'(0) < F_1'(0)$. If $R_0 < R_0^*$, from Theorem 2.2, we can know that there is no interaction between $F_1(B)$ and $F_3(B)$. Using $F_3'(0) < F_1'(0)$, we can get that all potential roots of $F_1(B) = 0$ are less than $\tilde{B}$. Thus, there is no positive equilibrium of system (2) when $R_0 < R_0^*$. Similarly, system (2) has no positive equilibrium if $c_2 \geq 0$.

Next let us consider the case for $c_2 < 0, R_0^* < R_0 < 1$. Based on Theorem 2.2, we find that $F_1(B)$ interacts with $F_3(B)$ at $B^{1b}$ and $B^{2b}$. Noting that $F_1(B^{1b}) < 0$ if $R_1 \leq 1$, it is easy to confirm that all potential positive roots of $F_1(B) = 0$ are not larger than $\tilde{B}$ when $R_1 \leq 1$. Therefore, system (2) has no positive equilibrium if $R_1 \leq 1$. If $R_1 > 1 > R_2$, it follows that $F_1(B^{1b}) > 0 > F_1(B^{2b})$ and we discuss the existence of positive equilibria in five cases:

(C1) Suppose $P_1 \leq 0$. Then $F_1(B)$ is a monotone increasing function, and (19) has a unique positive root $B_1$ which satisfies $B_1 > \tilde{B}$ and is a root of multiplicity 3 if $P_1 = 0, \Delta_1 = 0$. Therefore, system (2) has a unique equilibrium in this case. In particular, it is an equilibrium of multiplicity 3 as $P_1 = 0, \Delta_1 = 0$.

(C2) Suppose $P_1 > 0, B^{2b} \geq B_{12}$. Then $B_1$ is the unique positive root of (19) and is larger than $\tilde{B}$. Therefore system (2) has one positive equilibrium.

(C3) Suppose $P_1 > 0, B^{2b} < B_{12}, \Delta_1 > 0$. Then there only exists a positive root $B_1$ of (19) and it satisfies $B_1 > \tilde{B}$. Therefore, system (2) has a unique positive equilibrium.

(C4) Suppose $P_1 > 0, B^{2b} < B_{12}, \Delta_1 = 0$. Then $B_1$ and $B_2$ are two positive roots of (19) and both of them are larger than $\tilde{B}$. Furthermore, one of them is a root of multiplicity 2. Therefore system (2) has a simple positive equilibrium and a positive equilibrium of multiplicity 2.

(C5) Suppose $P_1 > 0, B^{2b} < B_{12}, \Delta_1 < 0$. Then there exist three positive roots $B_1, B_2, B_3$ of (19) and all of them are greater than $\tilde{B}$. Therefore system (2) has three positive equilibria (Figure 6).
For the other cases shown in Table 1, we can get the results for the existence of positive equilibria by the same method, and don’t present the proofs of these cases here for simplicity.

**Figure 6.** A profile graph of functions $F_1(B)$ and $F_3(B)$ defined in (19) and (B.50). The blue (red) line denotes $F_1(B)$ ($F_3(B)$).

**Appendix C. Supplementary to the proof of Theorem 3.3.** Here we aim to determine the sign of $M_{20}, M_{11} + 2L_{20}$. Using $F_1(\hat{B}) = F_1'(\hat{B}) = \Delta_1(\hat{B}) = 0$, we obtain

$$
\rho = \frac{(\theta \beta + \delta)(\sigma + \mu_1)K\mu_U\mu_2^2\hat{P}_2}{\beta B\hat{P}_1(2v\hat{B} - K\beta(v - \mu_B))(\mu_U + \beta \hat{B})},
$$

$$
\Lambda = -\frac{\beta \hat{B}\hat{P}_1(2v\hat{B} - K\beta(v - \mu_B))^2(\mu_U + \beta \hat{B})^3}{K^2\mu_U\mu_2^2\hat{P}_2(\sigma + \mu_1)(\theta \beta + \delta)^2},
$$

$$
N = -\frac{\mu_T\hat{P}_2(\theta \beta + \delta)(\sigma + \mu_1)\hat{B}^2(2v\hat{B} - K\beta(v - \mu_B) + v\mu_U)}{\beta \sigma \hat{P}_1(2v\hat{B} - K\beta(v - \mu_B))(\mu_U + \beta \hat{B})},
$$

where

$$
\hat{P}_1 = v\beta(\mu_U - \mu_T)\hat{B}^2 + \left(-\frac{1}{2}K\beta((v + \mu_T - \mu_B)\mu_U - \mu_T(v - \mu_B))
\right.
$$

$$
+ \frac{1}{2}v\mu_U^2\hat{B} + \frac{1}{2}K\mu_U^2\mu_T,
$$

$$
\hat{P}_2 = v\beta\hat{B}^2 - \frac{1}{2}K\beta(v + \mu_U - \mu_B)\hat{B} - \frac{1}{2}K\mu_U^2.
$$

Since $\rho, \Lambda, N > 0$, we have

$$
\hat{P}_1 > 0, \hat{P}_2 < 0, 2v\beta\hat{B} + K\beta(\mu_B - v) + v\mu_U < 0.
$$

Substituting (C.51) into $M_{11} + 2L_{20}, M_{20}$, we obtain

$$
M_{11} + 2L_{20} = \frac{\hat{P}_1(\Psi_2(\sigma + \mu_1) + \Psi_3)}{3|L|\mu_U^2\sqrt{\Delta_2}},
$$

$$
M_{20} = \frac{\sqrt{\Delta_2b_2K\mu_U^3}}{2|L|\alpha\hat{B}^2\hat{P}_2(2v\beta\hat{B} + K\beta(\mu_B - v) + v\mu_U)(\mu_U + \beta \hat{B})^2}.
$$
where
\[
\begin{align*}
|L| &= \frac{b_2(\hat{B})\sqrt{\Delta_2}\Psi_1}{4\alpha\hat{B}^3P_2(\mu + \beta\hat{B})^2 \left( v(\beta + v)\hat{B} + \frac{1}{2}K\beta(\mu_B - v) + \frac{1}{4}v\mu_U \right)^2}, \\
\Psi_1 &= (K\beta + v)\hat{B}\hat{P}_1 - \frac{1}{2}K\beta(\hat{B}(v + \mu_U - \mu_B) + (v - 3\mu_U - \mu_B))\hat{B}^2 \\
&\quad - K^2\beta\mu_U(v + \mu_U - \mu_B)\hat{B} - \frac{1}{2}K^2\mu_U^2, \\
\Psi_2 &= -\hat{P}_1 \left( v(\beta + v)\hat{B} - \frac{1}{2}(K\beta(v - \mu_B) - v\mu_U) \right) \\
\Psi_3 &= \alpha\hat{B}^3(\mu_U + \beta\hat{B})^2 \left( v\beta\hat{B} + \frac{1}{2}K\beta(v - \mu_B) - v\mu_U \right) + \frac{1}{2}K\beta\mu_U \left( v\beta\hat{B} \right), \\
Q_1 &= \frac{Kb_2\hat{P}_1\hat{P}_2(\mu_U + \beta\hat{B}) \left( v\beta\hat{B} - \frac{1}{4}(K\beta(v - \mu_B) - v\mu_U) \right) + \frac{1}{3}\hat{B}\beta\mu_U \left( v\beta\hat{B} \right)}{\mu_T} + \frac{1}{3}\beta\mu_U \left( v\beta\hat{B} \right), \\
M_3 &= \left( -\frac{1}{2}\hat{B}^3 K^3(v + \mu_U - \mu_B) + \frac{1}{2}\hat{B}^3 K^2(v + 6\mu_U - \mu_B) + v^3\mu_U \right. \\
&\left. - \frac{3}{2}v^2\beta \left( v - \frac{2}{3}\mu_U - \mu_B \right) \hat{B}^3 - \frac{3}{4}K^3\mu_U^2(v + 2\mu_U - \mu_B) \right) \\
&\left. + \left( -\frac{1}{4}\hat{B}^3 K^3(v + 6\mu_U - \mu_B)(v + \mu_U - \mu_B) + \frac{1}{4}\beta\mu_U K^2(v^2 - v(3\mu_U + 2\mu_B) \right) \\
&\left. + 10\mu_U^3 + 3\mu_U\mu_B + \mu_B^2) - \frac{1}{2}K\beta\mu_U(v - \mu_U - \mu_B) \right) \hat{B}^2. \\
\end{align*}
\]

As we have shown that $b_1(\hat{B}) > 0$, $b_2(\hat{B}) > 0$ hold for all positive equilibria, and
\[
b_1(\hat{B}) = -\frac{\hat{P}_2 \left( \hat{P}_1 + \frac{1}{2}\mu_T\mu_K(\mu + \mu_L) \right)}{\mu_U\hat{P}_1}, \quad b_2(\hat{B}) = -\frac{\mu_T(\mu + \mu_L)\Psi_1}{\hat{P}_1}, \\
\]
we get $\Psi_1 > 0$, thus $|L| > 0$. Using $|L| > 0$, it is easy to know that
\[
\text{sgn}(M_2) = -\text{sgn}(F''(\hat{B})), \quad \text{sgn}(M_1 + 2L_2) = -\text{sgn}(\Delta_2''(\hat{B})).
\]

### Appendix D. Supplementary to the proof of Theorem 3.4

Let $E^*(M^*_U, M^*_I, B^*, T^*)$ be the multiplicity 3 positive equilibrium. We have
\[
B^* = \frac{K\beta(v - \mu_B) - v\mu_U}{3v\beta}, \quad M^*_U = \frac{3v\Lambda}{K\beta(v - \mu_B) + 2v\mu_U}, \quad M^*_I = \frac{\mu_T}{\rho},
\]
\[
T^* = \frac{\rho K\beta(v - \mu_B) - v\mu_U - \mu_T(\mu + \mu_L)(K\beta(v - \mu_B) + 2v\mu_U)}{\alpha\mu_T(K\beta(v - \mu_B) + 2v\mu_U)}.
\]

Using $F_1(B^*) = F_1'(B^*) = b_3(B^*) = 0$, we obtain
\[
\Lambda = \frac{(K\beta(v - \mu_B) + 2v\mu_U)^3}{27K\beta\mu_Uv(\theta\beta + \delta)}, \quad \Lambda = \frac{(K\beta(v - \mu_B) + 2v\mu_U)^3}{27K\beta\mu_Uv(\theta\beta + \delta)}, \quad \Lambda = \frac{(K\beta(v - \mu_B) + 2v\mu_U)^3}{27K\beta\mu_Uv(\theta\beta + \delta)}.
\]

\[
N = \frac{\mu_T(\theta\beta + \delta)(\mu + \mu_L)(K\beta(v - \mu_B) - v\mu_U)^2}{\alpha\mu_T(K\beta(v - \mu_B) + 2v\mu_U)}.
\]
\[ \rho = \frac{27 K \beta \mu_U v^2 \mu_T^2 (\theta \beta + \delta)(\sigma + \mu_I)}{(K \beta (v - \mu_B) + 2v \mu_U)(K \beta (v - \mu_B) - v \mu_U) P_1^*}, \] (D.59)

where
\[ P_1^* = \mu_T (K \beta (v - \mu_B) + 2v \mu_U)(K \beta (v + 3\mu_U - \mu_B) - v \mu_U) - \mu_U (K \beta (v - \mu_B) - v \mu_U)^2. \] (D.60)

Substituting (D.59) into \( T^* \), we have
\[ T^* = \frac{(K \beta (3\mu_U + v - \mu_B) - v \mu_U) \mu_T - P_1^* (\sigma + \mu_I)}{\alpha P_1^*}. \] (D.61)

To ensure the positivity of \( \rho, T^* \), we need to have \( \mu_T > \max(\mu_T^{1*}, \mu_T^{2*}) \). Then using (D.59) and (D.60), we obtain
\[ M_{20} = 0, \quad M_{11} + 2L_{20} = \frac{-6v \beta S_{20}}{S_{21}(K \beta (v - \mu_B) - v \mu_U)}, \]
\[ M_{30} - M_{11}L_{20} = -\frac{v \beta \mu_U (\sigma + \mu_I) \mu_T (K \beta (v - \mu_B) - v \mu_U)^2}{P_1^* K b_2(B^*)}, \] (D.62)
in which
\[ b_2(B^*) = \frac{(\sigma + \mu_I) \mu_T S_{21}}{3v \beta K \beta P_1^*}, \]
\[ S_{20} = \frac{1}{2} \mu_T v (K \beta (3\mu_U + v - \mu_B) - v \mu_U)^2 (K \beta (v - \mu_B) + 2v \mu_U) + \mu_U (K \beta + \frac{1}{2} v)(K \beta (v - \mu_B) - v \mu_U)^3 > 0, \]
\[ S_{21} = K^4 \beta^4 (v - \mu_B)^2 (3\mu_U + v - \mu_B) - 3K^2 \beta^2 v^2 \mu_T^2 (v - \mu_B - 4\mu_U) + K^3 \beta^3 (v - \mu_B)((v - \mu_B)(v - \mu_B + 9\mu_U) + 12\mu_U) - 3K^2 \beta^2 \mu_T^2 \left( v + \frac{7}{3} (\mu_U - \mu_B) \right) + 2v^4 \mu_T^3 > 0. \] (D.63)

Thus,
\[ b_{11} < 0, \quad b_{30} < 0. \]

Appendix E. Symbolic description in system (44). Here, the forms of \( a_{30}, b_{21} \) and \( b_{40} \) shown in (44) are represented.
\[ a_{30} = L_{30} - L_{20}(L_{11} + M_{02}) - N_{30}, \]
\[ b_{21} = M_{21} - M_{02}M_{11} + 2L_{20}L_{11} - M_{02}L_{20} + 3N_{30} \]
\[ + (M_{11} + 2L_{20}) \left( \frac{1}{2}(L_{11} + M_{02}) - M_{02} \right), \]
\[ b_{40} = M_{40} - M_{02}M_{30} + N_{21}M_{20} + 2L_{20}L_{30} + 3N_{30}L_{20} \]
\[ + \frac{3b_{30}}{2} (L_{11} + M_{02}) - b_{11} \left( N_{30} - \frac{1}{2} L_{20}(L_{11} + M_{02}) \right) - b_{21}L_{20}, \] (E.64)
\[ N_{30} = -L_{20}(L_{11} + M_{02}) - M_{02}L_{20}, \quad N_{21} = 2L_{20}L_{02} + \frac{1}{2} M_{02}(L_{11} + M_{02}), \]
where
\[ M_{11} = \frac{3v^2 \beta P_1^*(K \beta (v - \mu_B) - v \mu_U) + 2\mu_T S_{51} S_{52}}{S_{21}(K \beta (v - \mu_B) - v \mu_U)}, \]
\[ L_{20} = -\frac{\mu_T}{{b_2}^2} P_1^* (K\beta(v - \mu_B) - v\mu_U)^2(\sigma + \mu_U), \]
\[ M_{02} = \frac{9v^2 \mu_T}{{b_2}^2} P_1 S_3 (K\beta(v + 3\mu_U - \mu_B) - v\mu_U)^2, \]
\[ M_{30} = \frac{3\beta^2 v^2 S_{32} S_{53} (K\beta(v - \mu_B) - v\mu_U)}{S_{21}^2}, \]
\[ L_{11} = \left(\sigma + \mu_U\right) \left(\frac{3}{2} v^2 \mu_T S_{34} + S_{35} + S_{36} + S_{37}\right) - P_1^* S_{32} (K\beta(v + 3\mu_U - \mu_B) - v\mu_U) S_{52} + \mu_U (K\beta(v - \mu_B) - v\mu_U)^3 (K\beta(v - \mu_B) + 2v\mu_U) + 6\mu_T \mu_U, \]
in which
\[ S_{33} = (K\beta)^3 (v - \mu_B)^2 + 2(K\beta)^2 (v(v - \mu_B) + 2\mu_U) - 3K\beta v^3 \mu_U (v - \mu_B - 2\mu_U) - v^3 \mu_U^2, \]
\[ S_{34} = (K\beta(v + 3\mu_U - \mu_B) - v\mu_U)^2 (K\beta(v - \mu_B) + 2v\mu_U) (K\beta(v - \mu_B) - v\mu_U), \]
\[ (K\beta)^2 (v - \mu_B)(v + 6\mu_U - \mu_B) + K\beta v\mu_U (v + 3\mu_U - \mu_B) - 2v^2 \mu_U^2, \]
\[ S_{35} = K^8 \beta^3 (v - \mu_B) (v - \mu_B + 3\mu_U) \left( (v - \mu_B + 3\mu_U)^2 - 3\mu_U \left( v - \mu_B + 3\mu_U \right) \right), \]
\[ + K^7 \beta^2 (v - \mu_B) \mu_U \left( (v - \mu_B + 3\mu_U)^3 + (v - \mu_B) (v - \mu_B + 3\mu_U)^2 - 3\mu_U (v - \mu_B - 3\mu_U) \right)^2 \left( v - \mu_B + 3\mu_U \right)^4, \]
\[ S_{36} = \frac{7(v - \mu_B)^2 K^6 \beta^6 \mu_U^2}{2} \left( (v - \mu_B - 3\mu_U)^4 - \frac{6\mu_U}{7} ((v - \mu_B - 3\mu_U)^3 \left( v - \mu_B - 3\mu_U \right) \right) \]
\[ - \left( v - \mu_B - 3\mu_U \right)^2 - 18 \frac{1}{7} (v - \mu_B + 2\mu_U) \right) \right) - 8K\beta v^4 \mu_U^4 \]
\[ \times \left( (v - \mu_B + 3\mu_U)^4 - 61 \frac{16}{61} (v - \mu_B - 3\mu_U)^3 - 61 \frac{16}{61} (v - \mu_B - 3\mu_U)^2 \right) \]
\[ + 9(23 \mu_B - 23v - 50 \mu_U) \right) \right), \]
\[ S_{37} = \frac{21}{2} \left( v - \mu_B + 3\mu_U \right)^4 - \frac{74\mu_U}{21} (v - \mu_B - 3\mu_U)^3 + \frac{165}{74} (v - \mu_B - 3\mu_U)^2 \]
\[ + \frac{6}{56} (21\mu_B - 19v - 51\mu_U) (v - \mu_B) (K\beta)^3 v^3 \mu_U^2 + 32 (K\beta)^3 v^3 \mu_U \left( v - \mu_B \right) \]
\[ - \frac{3\mu_U}{2} \right)^2 - 507 \frac{64}{61} (v - \mu_B - 3\mu_U)^2 - \frac{9\mu_U}{61} (180 \mu_B - 180v + 233 \mu_U), \]
\[ - \frac{33 K^2 \beta^2 v^5 \mu_U^5}{2} \left( (v - \mu_B)^2 + \frac{19(5\mu_B - 5v + 21\mu_U)}{33} \right) + 5v^8 \mu_U^2 \]
\[ - \frac{13 K\beta v^7 \mu_U^6}{2} \left( v - \mu_B + \frac{113}{13} \mu_U \right). \]
As the forms of $M_{21}, M_{40}, L_{30}$ are complex, we don’t present here.

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