ADV MATH SCI JOURNAL
Advances in Mathematics: Scientific Journal **9** (2020), no.9, 7269–7282
ISSN: 1857-8365 (printed); 1857-8438 (electronic)
https://doi.org/10.37418/amsj.9.9.76

BACKWARD BIFURCATION IN A WITHIN-HOST TUBERCULOSIS MODEL

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ABSTRACT. A within-host tuberculosis model describing the interaction between macrophages and Mycobacterium tuberculosis was developed and analyzed in this paper. We derive R_0 as the threshold value of the model and analyze the existence and stability of equilibrium points. Furthermore, bifurcation analysis performed based on the use of the application of the center manifold theory. Explicit condition for the existence of backward bifurcation is given. Finally, numerical simulations are presented to support the theoretical findings.

1. INTRODUCTION

Mycobacterium tuberculosis (Mtb) is an agent that causes Tuberculosis (TBC), an infectious disease that has a high mortality rate in various countries. Until now, tuberculosis is still one of the main causes of human death in the world. Based on the 2019 Global Tuberculosis Report released by WHO, eight countries that accounted for two-thirds of the total global TB cases were India (27 %), China (9 %), Indonesia (8 %), Philippines (6 %), Pakistan (6 %), Nigeria (4 %), Bangladesh (4 %) and South Africa (3 %) [1].

The Mtb bacteria commonly infect the lungs with alveolar macrophages as its primary target [2]. Responding to the presence of Mtb bacteria, the immune system forms granulomas consisting of immune cells known as macrophages which are responsible for controlling and separating the pathogens that infect

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2010 *Mathematics Subject Classification.* 34C23, 92B05.

Key words and phrases. Tuberculosis model, stability, backward bifurcation.

the lungs. Macrophages that function as the main host cell niche for the growth and survival of Mtb, are found in several organs of the human body [3, 4]. Macrophages ingest Mtb bacteria and isolate them in cellular compartments where bacteria cannot grow back. After the droplet core containing Mtb bacteria reaches the pulmonary alveoli, these bacteria are digested by alveolar macrophages and most can be destroyed or inhibited. A small amount can multiply intracellularly and is released when macrophages die. The dies macrophages do not necessarily cause bacteria to die but instead becomes a fuel for bacteria to grow. Living bacteria can spread through the lymphatic channels or through the bloodstream to distant tissues and organs, including areas of the body where TB disease is likely to develop, such as lymph nodes, lung spleen, kidneys, brain, and bones [5–7]. MTb does not have classical virulence factors and can remains on the host during long-term latency and will not cause transmission or significant damage if the host's immunity is not impaired [8].

In recent years mathematical models have been developed to describe the dynamics of tuberculosis in the human body, see [9–13]. In [9], Ibarguen-Mondragon et al. developed and analyzed a mathematical model that described dynamic interactions between macrophage cells, Mtb bacteria, and T-cell. Furthermore, Shi et al. in [10] added the chemotherapy drug variable and analyzed it with control theory. Recent research in [12] based on the model in [11] shows how T cell responses, which are immune cells to the presence of Mtb bacterial intervention. Bifurcation analysis is carried out to show conditions so that TB can disappear from the human body. Furthermore, Zhang et al. [13] added an analysis of global stability and conducted a bifurcation analysis for the disease-free equilibrium point. However, these models have not been able to clearly determine the important factors that play a role in TB infection. Motivated by this, in this article we simplified Zhang's model in [13] by combining T cells into a single immune response, which reacts against MTb bacteria that infect macrophages. Furthermore, in this study, we will investigate a qualitative analysis and show that the model undergoes a backward bifurcation. The bifurcation analysis in this study will be carried out based on the use of the center manifold theory as introduced by Castillo-Chavez and Song in [15].

This paper is organized as follows. We begin by formulating our model and establishing the properties of solutions in Section 2. In Section 3, we discuss the existence of equilibria and stability of the disease-free equilibrium point. In

section 4, we investigate the condition for the existence of backward bifurcation. To support the theoretical results, some numerical simulations are given in Section 5. Finally, discussion and conclusion are given in Section 6.

2. Model Formulation

Based on a within-host tuberculosis model in [13], we study a 3-dimensional ODE model that describes the interaction between uninfected macrophages (M_u), infected macrophages (M_i), and MTb bacteria (B). Our model is given as:

$$\begin{aligned} \frac{dM_u}{dt} &= \Lambda - \mu M_u - \frac{\beta M_u B}{1+\alpha B}, \\ \frac{M_i}{dt} &= \frac{\beta M_u B}{1+\alpha B} - cM_i - \frac{kM_i}{1+\varepsilon M_i}, \\ \frac{dB}{dt} &= rcM_i - \gamma M_u B - dB. \end{aligned} \tag{2.1}$$

In model (2.1), we assume that uninfected macrophages reproduce at a constant rate of Λ and decrease by a natural death at a rate of μ. Uninfected macrophages became infected at a saturated incidence rate of $\frac{\beta M_u B}{1+\alpha B}$, with β is the maximal transmission of infection rate, while $\frac{1}{1+\alpha B}$ is an inhibition effect. Inside the infected macrophages, MTb bacteria multiply up to a limit in which the infected macrophages bursts, followed by the release of new bacteria. In this model, c is the rate of macrophages burst and r is the average number of the MTb bacteria released by infected macrophages. The releasing bacteria then infect macrophages or ingested and killed by uninfected macrophages. The parameters γ and d are the MTb bacteria death rate by uninfected macrophages and MTb bacteria natural death rate. The infected macrophages die caused by the adaptive immune response which modeled in a density-dependent term,$\frac{kM_i}{1+\varepsilon M_i}$. In this model, k and ε are maximum killing rate and half-saturation constant, respectively.

The following theorem verifies that the system (2.1) has biological meaningful, that is, all solutions with nonnegative initial conditions remain nonnegative for all $t \geq 0$.

Theorem 2.1. *Let $\bar{\mu} = min\{\mu, c\}$. The set*

$$\Omega = \{(M_u, M_i, B) \in \mathbf{R}^3_+ : M_u + M_i \leq \frac{\Lambda}{\bar{\mu}}, B \leq \frac{d\bar{\mu}}{rc\Lambda}\}$$

is a positive invariant and attracting set for equation (2.1).

Proof. From the first equation of (2.1), we have

$$\frac{dM_u}{dt} \leq \Lambda - \mu M_u.$$

Thus, from standard comparison theorem we have $\lim_{t\to\infty}$ sup $M_u(t) \leq \frac{\Lambda}{\mu}$.

Let $M(t) = M_u(t) + M_i(t)$. Then we get

$$\begin{aligned}\frac{dM}{dt} &= \Lambda - \mu M_u - cM_i - \frac{kM_i}{1+\varepsilon M_i} \\ &\leq \Lambda - \mu M_u - cM_i \leq \Lambda - \bar{\mu},\end{aligned}$$

with $\bar{\mu} = min\{\mu, c\}$. Thus, we have

$$0 \leq M(t) \leq \frac{\Lambda}{\bar{\mu}}.$$

Clearly, $M_i \leq \frac{\Lambda}{\bar{\mu}}$.

From the third equation of (2.1), we have

$$\frac{dB}{dt} = rcM_i - \gamma M_u B - dB \leq rc\frac{\Lambda}{\bar{\mu}} - dB.$$

Hence, $\lim_{t\to\infty}$ sup $B(t) \leq \frac{rc\Lambda}{d\bar{\mu}}$. Therefore, all solution of (2.1) that starting in Ω remain in Ω for all $t \geq 0$. □

3. Existence and Stability of equilibria

In this sections, we will consider the existence and stability of the equilibrium points of system (2.1). The crucial quantity is the basic reproduction number that measures the expected number of secondary infections that result from one newly infected cell. Applying the procedure of next-generation matrix described in [14], we obtain

$$R_0 = \sqrt{\frac{rc\beta\Lambda}{(c+k)(\gamma\Lambda + d\mu)}}. \tag{3.1}$$

Then we get the following theorem.

Theorem 3.1. *Consider the system* (2.1).

(i) *If* $R_0 < 1$ *and* $c+k-\varepsilon\Lambda \geq 0$*, then the system* (2.1) *only has a disease free equilibrium* $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0\right)$.

(ii) *If* $R_0 < 1$ *and* $c+k-\varepsilon\Lambda < 0$*, in addition to* E_0*, then the system* (2.1) *may has two or no positive disease equilibrium points.*

(iii) *If* $R_0 > 1$*, in addition to* E_0*, the system* (2.1) *at least has one positive disease equilibrium point.*

Proof. Solving the system (2.1) by setting the right-hand side equal to zero, we get a disease-free equilibrium point, denoted by E_0, and it is given by

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0\right)$$

and disease equilibrium points, denoted by E^*_{1j}, and given by

$$E_{1j^*} = (M^*_u, M^*_i, B^*)\,,$$

with

$$M^*_u = \frac{\Lambda(1+\alpha B^*)}{\mu + (\alpha\mu - \beta)B^*}, M^*_i = \frac{(\gamma M^*_u + d)B^*}{rc}, \tag{3.2}$$

and B^* is any positive root of the qubic equations

$$a_3B^3 + a_2B^2 + a_1B + a_0 = 0, \tag{3.3}$$

where

$$\begin{aligned}
a_3 &= (\varepsilon\alpha^2(d^2\mu^2 + 2d\gamma\mu\Lambda + \gamma^2\Lambda^2) + \varepsilon\alpha(2d^2\mu\beta + 2d\gamma\Lambda\beta) + \varepsilon d^2\beta^2,\\
a_2 &= \alpha^2\mu r(cd\mu + \gamma c\Lambda + \mu kd + k\gamma\Lambda) + r\alpha\beta(c+k-\Lambda\varepsilon)(d\mu+\gamma\varepsilon)\\
&\quad +2d\Lambda\gamma\beta\varepsilon + (c+k)d\mu r\alpha\beta + \alpha\varepsilon(2d^2\mu^2 + 4d\Lambda\gamma\mu + 2\gamma^2\Lambda^2)\\
&\quad +rd\beta^2(c+k-\varepsilon\Lambda) + 2d^2\mu\beta\varepsilon,\\
a_1 &= r(\beta+\mu\alpha)(c+k)(d\mu+\Lambda\gamma)(1-R_0^2) + r\beta(c+k-\varepsilon\Lambda)(d\mu+\Lambda\gamma)\\
&\quad +r\mu\alpha(c+k)(d\mu+\Lambda\gamma) + \Lambda\gamma\varepsilon(\gamma\Lambda + 2d\mu)\\
a_0 &= r\mu(c+k)(d\mu+\Lambda\gamma)(1-R_0^2).
\end{aligned}$$

In order to get a positive disease equilibrium, the condition $M^*_u > 0$ must be hold. From (3.2), it is clear that $M^*_u > 0$ if only if $\mu + (\alpha\mu - \beta)B^*$ or $B^* < \frac{\mu}{\beta - \alpha\mu}$, with B^* is positive roots of equation (3.3). The coefficient a_3 in equation (3.3)

is always positive, while a_2, a_1, and a_0 can be positive or negative. Furthermore, we have

(i) If $R_0 < 1$ and $c + k - \varepsilon\Lambda \geq 0$, then both of the coefficients a_2 and a_1 are positive, so there are no changes of coefficient sign of equation (3.3). According the Descartes rule of sign, there are no positive real root of equation (3.3). Hence, the system (2.1) only has a disease-free equilibrium $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0\right)$.

(ii) If $R_0 < 1$ and $c + k - \varepsilon\Lambda < 0$, then the coefficient a_0 is always positive, while both a_1 and a_2 can be positive or negative. According the Descartes rule of sign, equation (3.3) may have two or no positive real roots. Therefore, in addition to E_0, then the system (2.1) may has two or no positive disease equilibrium points.

(iii) If $R_0 > 1$, the coefficient a_0 is always negative. Since a_3 is always positive, at least there is one change of coefficient sign of equation (3.3). According the Descartes rule of sign, there is at least one positive root of equation (3.3). The possible changes of sign for the coefficient of equation (3.3) can be determined from Table 1. Therefore, in addition to E_0, the system (2.1) at least has one positive disease equilibrium point.

This completes the proof.

□

TABLE 1. Sign of the coefficients of equation (3.3) for $R_0 > 1$.

a_3	a_2	a_1	a_0
$+$	$+$	$+$	$-$
$+$	$+$	$-$	$-$
$+$	$-$	$+$	$-$
$+$	$-$	$-$	$-$

The following theorem shows that R_0 is a threshold quantity for the stability of disease-free equilibrium point of system (2.1). The stability determined by the sign of real part of eigenvalues of the Jacobian matrix at the given equilibrium point.

Theorem 3.2. *The disease-free equilibrium* $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0\right)$ *is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof. The Jacobian matrix of system (2.1) at $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0\right)$ is

$$J(E_0) = \begin{bmatrix} -\mu & 0 & -\frac{\beta\Lambda}{\mu} \\ 0 & -(c+k) & \frac{\beta\Lambda}{\mu} \\ 0 & rc & -\frac{\gamma\Lambda+d\mu}{\mu}. \end{bmatrix}.$$

that gives the following characteristic equation

$$(\lambda+\mu)(\lambda^2 + P_1\lambda + P_0) = 0. \tag{3.4}$$

where

$$\begin{aligned} P_1 &= k + c + \frac{\gamma\Lambda + d\mu}{\mu} \geq 0, \\ P_0 &= \frac{(k+c)(\gamma\Lambda + d\mu) - rc\beta\Lambda}{\mu}. \end{aligned}$$

It is clear that all eigenvalues have negative real part if $P_0 > 0$, that is $(k+c)(\gamma\Lambda + d\mu) - rc\beta\Lambda > 0$ or $\frac{rc\beta\Lambda}{(k+c)(\gamma\Lambda+d\mu)} < 1$. It implies that the disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. □

Now, consider the critical case $R_0 = 1$. It implies that $rc\beta\Lambda = (k+c)(\gamma\Lambda+d\mu)$. In this case the characteristic equation (3.4) has two negative eigenvalues and one zero eigenvalue. In the next section, we will use the application of center manifold theorem introduced in [15] to study the stability of the equilibrium point E_0.

4. THE EXISTENCE OF BACKWARD BIFURCATION

Based on the formula of basic reproduction number, R_0 in (3.1), we find that the stability of equilibrium point significantly affected by the transmission of infection rate β, the average number of the MTb bacteria r, and the rate of macrophages burst c. In this section, we investigate the effect of parameters to the number of equilibrium points and their stability change by varying the parameters value. We thus choose the transmission of infection rate β as a bifurcation parameter and derive the sufficient conditions for the occurrence of backward and forward bifurcation. We have the following theorem.

Theorem 4.1. *The system* (2.1) *in* $R_0 = 1$ *exhibits backward bifurcation if* $k\Lambda\varepsilon\mu^2 - 1 + \Lambda(c+k)(\gamma - \alpha\beta) > 0$.

Proof. From (3.1) we find that $R_0 = 1$ iff $\beta = \beta^* = \frac{(k+c)(\gamma\Lambda+d\mu)}{rc\Lambda}$ and E_0 is locally asymptotically stable if $\beta < \beta^*$, whereas it loses its stability if $\beta > \beta^*$. Evaluating the eigenvalues of the Jacobian matrix of system (2.1) at (E_0, β^*) we get $\lambda_1 = -\mu, \lambda_2 = 0$, and $\lambda_3 = -\frac{\mu(c+k)(\gamma\Lambda+d\mu)}{\mu}$. It is clear that $\lambda_2 = 0$ is a single zero eigenvalue and the others eigenvalues are real and negative. Hence, E_0 is a non hyperbolic equilibrium point and the system (2.1) can undergo backward bifurcation at $\beta = \beta^*$. Furthermore, we can determine the eigenvector associated with the zero eigenvalue.

Let $\mathbf{w} = (w_1, w_2, w_3)^T$ be the right eigenvector of the Jacobian matrix $J(E_0, \beta^*)$. We have

$$\begin{aligned} -\mu w_1 - \frac{(c+k)(\gamma\Lambda+d\mu)}{\mu rc} w_3 &= 0, \\ -(c+k)w_2 + \frac{(c+k)(\gamma\Lambda+d\mu)}{\mu rc} w_3 &= 0, \\ rcw_2 - \frac{(\gamma\Lambda+d\mu)}{\mu} w_3 &= 0. \end{aligned}$$

Then we get

$$\mathbf{w} = \left(-\frac{(c+k)(\gamma\Lambda+d\mu)}{\mu^2 rc}, \frac{\gamma\Lambda+d\mu}{\mu rc}, 1 \right). \tag{4.1}$$

The left eigenvector of the Jacobian matrix $J(E_0, \beta^*)$ satisfying $\mathbf{v}.\mathbf{w} = 1$ is given by

$$\mathbf{v} = \left(0, -\frac{\mu^2 rc}{(c+k)(\gamma\Lambda+d\mu)}, \frac{\mu}{\gamma\Lambda+d\mu+\mu} \right). \tag{4.2}$$

Now, we define the coefficient a and b:

$$a = \sum_{i,j,k=1}^{3} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0, \beta^*), \quad b = \sum_{i,k=1}^{3} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(E_0, \beta^*).$$

In view of (4.1), (4.2), and

$$\begin{aligned} f_1 &= \Lambda - \mu M_u - \frac{\beta M_u B}{1+\alpha B}, \\ f_2 &= \frac{\beta M_u B}{1+\alpha B} - cM_i - \frac{kM_i}{1+\varepsilon M_i}, \\ f_3 &= rcM_i - \gamma M_u B - dB, \end{aligned}$$

we then get

$$a = \frac{2(\gamma\Lambda + d\mu)\kappa}{\Lambda\mu rc(c+k)(\gamma\Lambda + d\mu + \mu)}$$

with $\kappa = \Lambda\varepsilon k\mu^2 - 1 + \Lambda(c+k)(\gamma - \alpha c)$ and

$$b = \frac{\Lambda rc}{(c+k)(\gamma\Lambda + d\mu + \mu)}.$$

We find that b is always positive. Next, by applying the Theorem 4 in [15], we conclude that the system (2.1) exhibits a backward bifurcation if $\kappa > 0$, i.e $\Lambda\varepsilon k\mu^2 - 1 + \Lambda(c+k)(\gamma - \alpha c) > 0$. Otherwise, forward bifurcation is occur. This completes the proof. □

The existence of backward bifurcation plays an important role in a management of disease. The backward bifurcation shows that a stable disease-free equilibrium coexist with both a stable and unstable disease equilibrium. Biologically, the backward bifurcation at $R_0 = 1$ makes treatment more difficult, because the condition $R_0 < 1$ is not completely sufficient to eradicate infectious cases.

5. NUMERICAL SIMULATIONS

In this section, we give some numerical simulations to demonstrate the theoretical results in the previous section. In the simulation, we use the parameter values obtained from literature [13]. We consider a set of parameter values:

$$\begin{aligned} &\Lambda = 3500, \mu = 0.01, \beta = 0.8 \times 10^{-8}, \alpha = 0.01, c = 0.3, \\ &k = 1, \epsilon = 30, r = 30, \gamma = 0.125 \times 10^{-8}, d = 0.05. \end{aligned} \tag{5.1}$$

With these set of parameter values, the condition of Theorem 3.1(ii) is satisfied. We have $R_0 = 0.61994 < 1$, $c + k - \varepsilon\Lambda = -1.0499 \times 10^5 < 0$ and $E_0 = (350000, 0, 0)$. From Theorem 3.2 we know that E_0 is locally asymptotically stable, see Figure 1. In this case, the system (2.1) has no positive disease equilibrium point. Figure 1 confirm that all trajectories approach to the equilibrium point E_0.

Now, we will analyze the effect of variation in parameter β and keeping all other parameters fixed as given in (5.1). We found that, if $0 < \beta < 2.0815476 \times 10^{-8}$, then $c+k-\varepsilon\Lambda < 0$ and $R_0 < 1$. We noticed that, if $0 < \beta < 0.9619088 \times 10^{-8}$, then the equation (3.3) has no positive real root, so the system (2.1) has no positive disease equilibrium point. If $0.9619088 \times 10^{-8} < \beta < 2.0815476 \times 10^{-8}$,

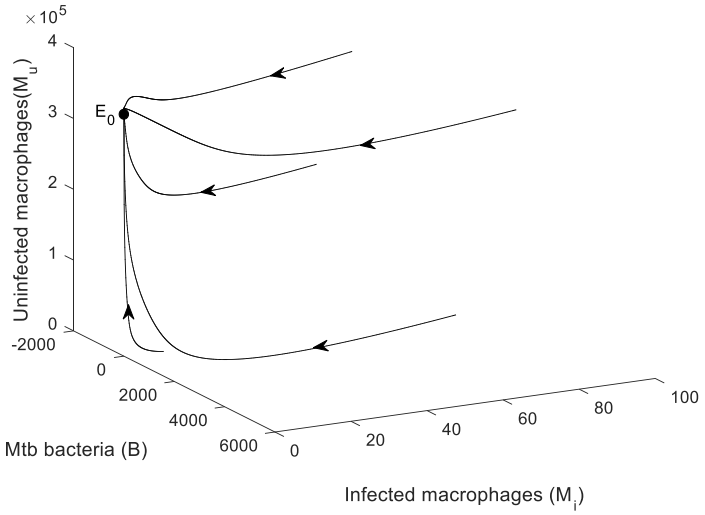

FIGURE 1. The system (2.1) has only one disease free equilibrium $E_0 = (3.5 \times 10^5, 0, 0)$ and it is locally asymptotically stable.

then the equation (3.3) has two positive real roots, so the system (2.1) has two positive disease equilibrium points. As illustration in Figure 4, with $\beta = 1.08 \times 10^{-8}$, in addition to $E_0 = (3.5 \times 10^5, 0, 0)$ we found two disease equilibrium points, i.e unstable equilibrium point $E_{11}^* = (3.49995 \times 10^5, 0.082393, 14.702156)$ and stable equilibrium point $E_{12}^* = (3.49998 \times 10^5, 0.47267, 84.34271)$.

If we set $\beta = 2.28 \times 10^{-8}$, we have $R_0 = 1.04658 > 1$ and the condition of Theorem 3.1(iii) is satisfied. From Theorem 3.2, we know that the disease-free equilibrium point E_0 is unstable. The system (2.1) has only one stable disease equilibrium $E_{11}^* = (3.49937 \times 10^5, 1.9586, 349.4906)$. Figure 3 confirm that all trajectories approach the equilibrium point E_{11}^*.

Finally, we find that with the set of parameter values as in (5.1), the condition in Theorem 4.1 is satisfied, that is $k\Lambda\varepsilon\mu^2 - 1 + \Lambda(c + k)(\gamma - \alpha\beta) = 9.5 > 0$. If the equilibrium point E_0 continued with respect to parameter β, then the system(2.1) exhibits a backward bifurcation at $R_0 = 1$ associated with $\beta = \beta^* = 2.0815476 \times 10^{-8}$. Subsequently, there is a saddle-node bifurcation at $\beta = \beta^* = 0, 961908 \times 10^{-8}$ since the number of disease equilibrium point changes from one to three as β passes through this point. Figure 4 shows that bistable behaviour exist whenever $0, 961908 \times 10^{-8} < \beta < 2.0815476 \times 10^{-8}$. In this interval, both

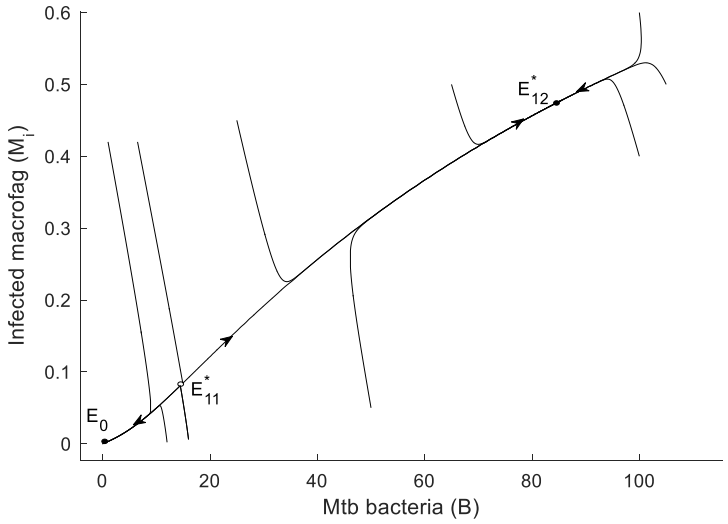

FIGURE 2. Phase portraits Infected macrofag vs Mtb bacteria with $\beta = 1.08 \times 10^{-8}$ The system (2.1) has one disease-free equilibrium $E_0 = (3.5 \times 10^5, 0, 0)$ and it is locally asymptotically stable.

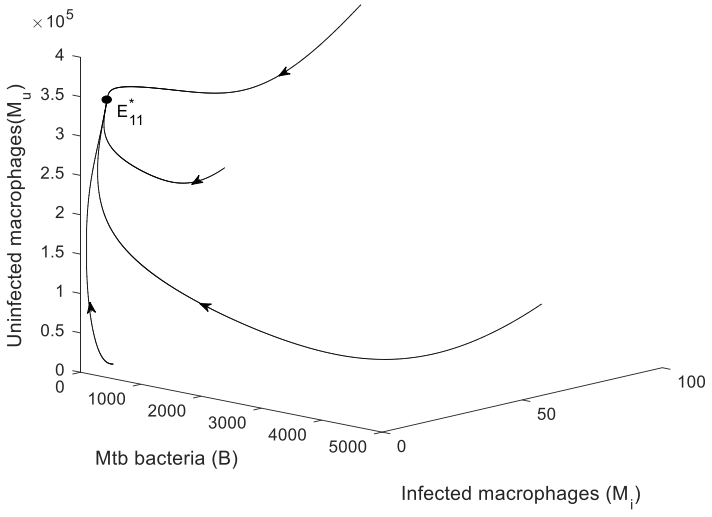

FIGURE 3. Phase portraits confirm that the system (2.1) has one stable disease equilibrium point E_{11} whenever $\beta = 2.28 \times 10^{-8}$.

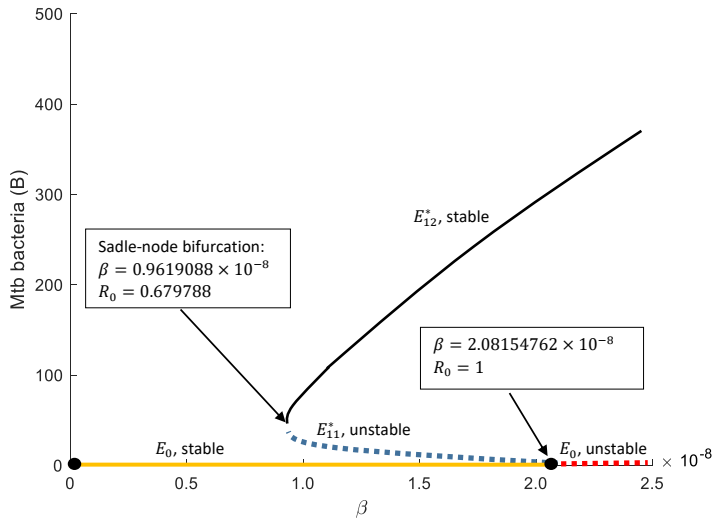

FIGURE 4. Backward bifurcation at $\beta = \beta^* = 2,0815476 \times 10^{-8}$.

the disease-free equilibrium point E_0 and the disease equilibrium point E_{12}^* are stable, while the disease equilibrium point E_{11}^* is unstable. Such conditions indicate that to eliminate the disease, it is not sufficient to reduce R_0 below 1. From Figure 4 , we know that, β must below $0,961908 \times 10^{-8}$, associated with R_0 below 0.679788 to guarantee that the system (2.1) has only disease-free equilibrium E_0.

6. DISCUSSION AND CONCLUSION

In this paper, we have studied a within-host tuberculosis model describing the interaction between Microbacterium tuberculosis and macrophages. The dynamics of the model depends on the stability of the equilibrium points. In order to determine the TBC treatment, we have to find the analytical condition so that all of the trajectories converge to the disease-free equilibrium. This condition is given in Theorem ref th-01. We found the threshold value R_0, so that the disease free equilibrium E_0 is stable when $R_0 < 1$ and unstable when $R_0 > 1$. Medically, if all of the trajectories converge to disease-free equilibrium, then Mtb bacteria and infected macrophage will eliminate so that the patient is ultimately cured of TBC. Meanwhile, if trajectories converge to the disease

equilibrium E^*_{1j}, then Mtb bacteria and infected macrophage will persist in the body.

Further, with the help of bifurcation analysis, we have shown that the continuation of the diseases free equilibrium point E_0 with respect to the parameter β, causes the system (2.1) undergoes a backward bifurcation at $R_0 = 1$. Through studying the backward bifurcation in our model we know that the basic reproduction number below unity is not fully adequate to eradicate the disease. From this result, we suggest that in order to successfully eradicate the disease, it is necessary to optimize and improve the efficiency of treatment that can reduce Mtb bacterial transmission. In other words, medical methods and technology need to be improved. A more realistic in-host TB model can also be found by selecting the most relevant treatment method with respect to actual data, so it can help clinicians to suggest the right treatment for TB patients. We will learn more in future research.

ACKNOWLEDGMENT

The authors would like to thank the editor and the anonymous referees for their careful reading the original paper and their valuable comments to the improvement of this work. This work is supported by the University of Ahmad Dahlan.

REFERENCES

[1] WHO : *Global tuberculosis report 2019*, WHO, 2019.

[2] A. AZAD, A. PAPP, X. ZHOU, ET AL. : *Alveolar macrophages responses to Mycobacterium tuberculosis reveal human to human variation in important immunobiology pathways gleaned from functional genomics study*, The J. Immunology, **202**(1) (2019), ID62:4.

[3] J. I. MOLIVA, J. TURNER, J. B. TORRELLES : *Immune Responses to Bacillus Calmette-Guerin Vaccination: Why Do They Fail to Protect against Mycobacterium tuberculosis?*, Front. Immunol., **8**(407) (2017), doi: 10.3389/fimmu.2017.00407.

[4] E. GUIRADO, L. S. SCHLESINGER, G. KAPLAN : *Macrophages in Tuberculosis: Friend or Foe*, Semin Immunopathol **35**(5) (2013), 563–583.

[5] E. GUIRADO, L. S. SCHLESINGER: *Modeling the Mycobacterium tuberculosis granuloma–the critical battlefield in host immunity and disease*, Front. Immunol., **4**(98) (2013), doi:10.3389/fimmu.2013.00098.

[6] D. MAHAMED, M. BOILLE, Y. GANGA, ET AL.: *Intracellular growth of Mycobacterium tuberculosis after macrophage cell death leads to serial killing of host cells*, eLife (2017);6:e22028 doi: 10.7554/eLife.22028.

[7] S. B. COHEN, B. H. GERN, J. L. DELAHAYE, K. N. ADAMS, C. R. PLUMLEE, J. WINKLER, D. R. SHERMAN, M. Y. GERNER, K. B. URDAH : *Alveolar macrophages provide an early Mycobacterium tuberculosis niche and initiate dissemination*, Cell Host Microbe, **24** (3) (2018), 439446.e4. doi:10.1016/j.chom.2018.08.001.

[8] Q. CHAI, Y. ZHANG, C. H. LIU : *Mycobacterium tuberculosis: An Adaptable Pathogen Associated With Multiple Human Diseases*, Front. Cell. Infect. Microbiol., **8**(158) (2018), doi: 10.3389/fcimb.2018.00158.

[9] E. IBARGUEN-MONDRAGON, L. ESTEVA, L. CHAVEZ-GALAN: *A mathematical model for cellular immunology of tuberculosis*, Math Biosci Eng., **8**(4) 2011), 973 – 986. doi: 10.3934/mbe.2011.8.973.

[10] R. SHI, Y. LI, S. TANG : *A Mathematical Model with Optimal Controls for Cellular Immunology of Tuberculosis*, Taiwanese Journal of Mathematics, **18**(2) (2014), 575 – 597.

[11] Y. DU, J. WU, J. M. HEFFERNAN : *A simple in-host model for Mycobacterium tuberculosis that captures all infection outcomes*, Math. Popul. Stud., **24**(1) (2017), 37 – 63.

[12] W. ZHANG : *Analysis of an in-host tuberculosis model for disease control*, Applied Mathematics Letters, **99** (2020), https://doi.org/10.1016/ j.aml.2019.07.014.

[13] W. ZHANG, F. FRASCOLI, J. M. HEFFERNAN : *Analysis of solutions and disease progressions for a within-host tuberculosis model*, Mathematics in Applied Sciences and Engineering, **1**(1) (2020), 39 – 49.

[14] P. VAN DEN DRIESSCHE, J. WATMOUGH : *Reproduction Numbers and sub-threshold endemic equilbria for compartmental model of disease transmission*, Mathematical Biosciences, **180** (2002), 29 – 48.

[15] C. CASTILLO-CHAVEZ, B. SONG:*Dynamical Model of Tubercolosis and Their Applications*, Math. Biosci. Eng., **1**(2) (2004), 361 – 404.

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