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Analysis of an in-host tuberculosis model for disease control

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ABSTRACT

Tuberculosis is still a global threat to humans. In this letter, we analyzed a four-dimensional with-in host tuberculosis infection model and obtain thresholds for basic reproduction number, forward bifurcation, and backward bifurcation. Global sensitivity analysis provides parameters, which significantly influence the model dynamics. Bifurcation analysis and diagrams show parameter regions for disease elimination, latency, and active disease. Numerical simulations prove analytical results and demonstrate bistable model dynamics.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTb) infection, has been a leading infectious disease with high mortality for centuries [1]. With the AIDS epidemic [2] and drug resistance [3], the re-emergence of TB is still a major global health threat in humans [4]. Based on an established model in [5], we study a 4-dimensional ODE host-pathogen TB model (1.1), which incorporates adaptive immune response. Our analysis and simulations demonstrate different infection outcomes. Model (1.1) includes uninfected and infected MTb target cells, (macrophages denoted as M_u and M_i) MTb population (B), and CD4+ T cells (T). The activation, infection and death rates of uninfected macrophages (M_u) are denoted as s_M, β and μ_M. Because the intracellular bacteria multiplication reaches a upper limit, infected macrophages burst at a rate of b. Infected macrophages also die because of the activated adaptive immune response, which is modelled as $\gamma M_i \frac{T}{T+c}$ [6] and γ representing the cell-mediated immune response rate. The recruitment of extracellular bacteria (B) is from cell division or from release of infected macrophage apoptosis. The bacteria division is modelled in a logistic form $\delta B(1-\frac{B}{K})$ with a constant growth rate (δ) and a carrying capacity (K). The death of an infected macrophage contributes to N_1 or N_2 extracellular bacteria by burst or adaptive immune response. While, extracellular bacteria (B) leave the system through killing and engulfment by uninfected macrophages at rates of η and N_3. Adaptive immune response is represented by CD4+ T cells (T), which

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produce cytokines, eliminate infected macrophages via activating CD8 T cells, and amplify the host immune response. The adaptive immune response is modelled by a density-dependent term, $\gamma M_i \frac{T}{T+c}$, where γ and c are maximum killing rate and half-saturation constant, respectively. The natural recruitment and death rates of activated CD4+ T cells are denoted as s_T and μ_T. Both infected macrophages (M_i) and extracellular bacteria (B) can activate CD4+ T cells (T), which are modeled by density-dependent terms as $\frac{c_M M_i T}{e_M T+1}$ and $\frac{c_B B T}{e_B T+1}$ with maximum rates c_M and c_B and saturating factors e_M and e_B. Our host-pathogen TB model is written as

$$\begin{aligned}
&\frac{dM_u}{dt} = s_M - \mu_M M_u - \beta M_u B, \qquad \frac{dM_i}{dt} = \beta M_u B - bM_i - \gamma M_i \frac{T}{T+c},\\
&\frac{dB}{dt} = \delta B\left(1-\frac{B}{K}\right) + M_i\left(N_1 b + N_2\gamma\frac{T}{T+c}\right) - M_u B\left(\eta + N_3\beta\right),\\
&\frac{dT}{dt} = s_T + \frac{c_M M_i T}{e_M T+1} + \frac{c_B B T}{e_B T+1} - \mu_T T.
\end{aligned} \tag{1.1}$$

2. Basic properties of solutions

2.1. Biological feasible region for solutions

First, we show that model (1.1) is well posed, that is nonnegative initial data generate nonnegative solutions. That means the nonnegative cone of $\mathbb{R}^4_+$ is positively invariant with respect to model (1.1). The vector field on the boundaries of $\mathbb{R}^4_+$ has the following properties $\frac{dM_u}{dt}|_{M_u=0} = s_M > 0$, $\frac{dM_i}{dt}|_{M_i=0} = \beta M_u B \geq 0$, $\frac{dB}{dt}|_{B=0} = M_i\left(N_1 b + N_2\gamma\frac{T}{T+c}\right) \geq 0$, $\frac{dT}{dt}|_{T=0} = s_T > 0$. Therefore, on the M_i-B-T, M_u-B-T, M_u-M_i-T, and M_u-M_i-B hyperplanes, vector fields are either tangent to the hyperplane or point to the interior of the nonnegative cone of $\mathbb{R}^4_+$. $\frac{dM_u}{dt}|_{M_u=0} = s_M > 0$ and $\frac{dT}{dt}|_{T=0} = s_T > 0$ imply that the host immune system is able to generate immune cells as a response against the infection even in the absence of uninfected macrophages and CD4+ T cells. While $\frac{dM_i}{dt}|_{M_i=0} \geq 0$ and $\frac{dB}{dt}|_{B=0} \geq 0$ implies that the existence of MTb infected macrophages or MTb bacteria can potentially lead to the development of the infection.

Next, we prove that solutions are bounded in the nonnegative cone of $\mathbb{R}^4_+$. Adding up the first two equations in model (1.1) gives $\frac{dM_u}{dt} + \frac{dM_i}{dt} = s_M - \mu_M M_u - bM_i - \gamma M_i \frac{T}{T+c} \leq s_M - \min\{\mu_M, b\}(M_u + M_i)$. It follows $(M_u + M_i)(t) \leq \frac{s_M}{\min\{\mu_M, b\}} \triangleq \mathcal{M}$. Since $0 < \frac{T}{T+c} < 1$, we have $\frac{dB}{dt} < \delta B - \frac{\delta}{K}B^2 + M_i(N_1 b + N_2\gamma) - M_u B(\eta + N_3\beta)$. Suppose that $B(t)$ is unbounded, that means $\lim_{t\to\infty} B(t) = +\infty$. Then there exists a sufficiently large time t_1, such that $\frac{dB}{dt} < \delta B + M_i(N_1 b + N_2\gamma) - \frac{\delta}{K}B^2 - M_u B(\eta + N_3\beta) < 0$, for all $t > t_1$, since the amplitude of second order term of B increases faster than lower order terms. With a negative changing rate $\frac{dB}{dt} < 0$, $B(t)$ decreases for $t > t_1$ until $\frac{dB}{dt} > 0$. Therefore B can not grow unbounded, which contradicts with the unbounded assumption. Therefore the total MTb bacteria load is bounded and denoted as $B(t) < \mathcal{B}$ for all $t > 0$. Because of $\frac{dT}{dt} < s_T + \frac{c_M}{e_M}M_i + \frac{c_B}{e_B}B - \mu_T T < s_T + \frac{c_M}{e_M}\mathcal{M} + \frac{c_B}{e_B}\mathcal{B} - \mu_T T$, for all $t > 0$, CD4+ T cell load $T(t)$ is bounded as well, that is $T(t) < \frac{1}{\mu_T}\left(s_T + \frac{c_M}{e_M}\mathcal{M} + \frac{c_B}{e_B}\mathcal{B}\right)$. The solutions of the in-host TB model (1.1) are well-posed and bounded for all time, which is summarized in the following theorem.

Theorem 1. *If initial conditions $M_u(0)$, $M_i(0)$, $B(0)$, and $T(0)$ are nonnegative, then the solution $M_u(t)$, $M_i(t)$, $B(t)$, $T(t)$ of model (1.1) stays in the positively invariant cone $\mathbb{R}^4_+$ and is bounded in the region*

$$\begin{aligned}
\Omega = \Bigg\{&(M_u, M_i, B, T) \in \mathbb{R}^4_+ | (M_u + M_i)(t) \leq \frac{s_M}{\min\{\mu_M, b\}}, B(t) < \mathcal{B},\\
&T(t) < \frac{1}{\mu_T}\left(s_T + \frac{c_M}{e_M}\mathcal{M} + \frac{c_B}{e_B}\mathcal{B}\right)\Bigg\}.
\end{aligned}$$

2.2. Equilibrium solutions

Sequentially, we solve $\frac{dM_u}{dt}=0$ and $\frac{dM_i}{dt}|_{\bar{M}_u}=0$, which yield $\bar{M}_u=\frac{s_M}{\beta\,\bar{B}+\mu_M}$ and $\bar{M}_i=\frac{\beta\,s_M\bar{B}(\bar{T}+c)}{(\beta\bar{B}+\mu_M)(b\,c+b\,\bar{T}+\gamma\bar{T})}$. Then, solving $\frac{dB}{dt}|_{\bar{M}_u,\,\bar{M}_i}=0$ results $\bar{B}_0=0$ or

$$\bar{T}=\frac{-c(((\beta\bar{B}+\mu_M)\delta+((N1-N3)\beta-\eta)s_M)K-\delta\bar{B}(\beta\bar{B}+\mu_M))b}{((\gamma+b)(\beta\bar{B}+\mu_M)\delta+(((N1-N3)b+\gamma(N2-N3))\beta-\eta(\gamma+b))s_M)K-\delta\bar{B}(\gamma+b)(\beta\bar{B}+\mu_M)}.$$

Last, considering $\frac{dT}{dt}|_{\bar{M}_u,\,\bar{M}_i,\,\bar{B}_0}=0$, we have a disease-free equilibrium (DFE) written as $\bar{E}_0$: ($\bar{M}_{u0}$, $\bar{M}_{i0}$, $\bar{B}_0$, $\bar{T}_0$)=($\frac{s_M}{\mu_M}$, 0, 0, $\frac{s_T}{\mu_T}$). Moreover, $\frac{dT}{dt}|_{\bar{M}_u,\,\bar{M}_i,\,\bar{T}}=0$ gives an infected equilibrium $\bar{E}_1$: ($\bar{M}_u$, $\bar{M}_i$, $\bar{B}$, $\bar{T}$), where $\bar{B}$ is determined by

$$f(\bar{B})=\frac{dT}{dt}|_{\bar{M}_u,\bar{M}_i,\bar{T}}=[c_B\bar{T}(e_M\bar{T}+1)]\bar{B}+[-e_M\,\mu_T\bar{T}^2+(c_M\bar{M}_i+e_M\,s_T-\mu_T)\bar{T}+s_T](e_B\bar{T}+1)=0. \quad (2.1)$$

3. Thresholds for disease free equilibrium

In this section, we will study two thresholds for the disease progression. We will first calculate the basic reproduction number and then the condition for forward and backward bifurcations.

3.1. The basic reproduction number

Applying the next-generation matrix approach [7], we classify the state variables in model (1.1) as the infection classes (M_i, B) and anti-infection classes (M_u, T). Then the basic reproduction number is

$$\mathcal{R}_0=\rho(FV^{-1})=\frac{\delta\,\mu_M}{2\,(N_3\,\beta+\eta)\,s_M}+\frac{1}{2}\sqrt{\frac{4\,\beta\,(c\,\mu_T+s_T)\left(N_1\,b+\frac{N_2\,\gamma\,s_T}{\mu_T\,c+s_T}\right)}{(N_3\,\beta+\eta)(b\,c\,\mu_T+b\,s_T+\gamma\,s_T)}+\frac{\delta^2\,\mu_M^2}{(N_3\,\beta+\eta)^2\,s_M^2}},$$

where $F=\begin{bmatrix}0 & \frac{s_M}{\mu_M}\beta\\ N_1\,b+\frac{N_2\,\gamma\,s_T}{\mu_T\left(\frac{s_T}{\mu_T}+c\right)} & \delta\end{bmatrix}$, $V=\begin{bmatrix}b+\frac{\gamma\,s_T}{\mu_T\,c+s_T} & 0\\ 0 & \frac{s_M(N_3\,\beta+\eta)}{\mu_M}\end{bmatrix}$, ρ denotes the spectral radius. The following theorem follows immediately from Theorem 2 in [7].

Theorem 2. *The DFE $\bar{E}_0$ is locally asymptotically stable if $\mathcal{R}_0<1$, and unstable if $\mathcal{R}_0>1$.*

3.2. The threshold for forward and backward bifurcations

To study the dynamics at $\mathcal{R}_0=1$, we rewrite model (1.1) in a general form as

$$\frac{dx}{dt}=f(x,\phi),\qquad f:\mathbb{R}^4\times\mathbb{R}^r\to\mathbb{R}^4, \quad (3.1)$$

where $x=(M_u,\,M_i,\,B,\,T)$, ϕ denotes all r positive parameters in model (1.1), and $f\in\mathbb{C}^2(\mathbb{R}^4\times\mathbb{R}^r)$. The DFE $\bar{E}_0$ is denoted as x_0, that is $f(x_0,\,\phi)\equiv 0$, for all parameters ϕ.

Theorem 3. *At $\mathcal{R}_0=1$, the Jacobian matrix of model (1.1) at the DFE $\bar{E}_0$ has a single zero eigenvalue (that is $D_xf(x_0,\phi)|_{R_0=1}$ has one zero eigenvalue). Moreover all other eigenvalues have negative real parts under certain parameter conditions.*

Proof. The linearized matrix of system (3.1) evaluated at the equilibrium $x = x_0$ is denoted as

$$D_x f(x_0, \phi) = \begin{bmatrix} -\mu_M & 0 & -\dfrac{\beta\, s_M}{\mu_M} & 0 \\ 0 & -b - \dfrac{\gamma\, s_T}{s_T + \mu_T\, c} & \dfrac{\beta\, s_M}{\mu_M} & 0 \\ 0 & N_1\, b + \dfrac{N_2\, \gamma\, s_T}{s_T + \mu_T\, c} & \delta - \dfrac{sM}{\mu_M}\,(N_3\, \beta + \eta) & 0 \\ 0 & \dfrac{c_M\, s_T}{e_M\, s_T + \mu_T} & \dfrac{c_B\, s_T}{e_B\, s_T + \mu_T} & -\mu_T \end{bmatrix}. \tag{3.2}$$

Eigenvalues of $D_x f(x_0, \phi)$ evaluated at $\mathcal{R}_0 = 1$ are 0, $-\mu_T$, $-\mu_M$, and Ev_4, where

$$Ev_4 = -\frac{((N_3\, \beta + \eta)\,(N_3\, \beta - \eta)\, s_M^2 + \delta^2\, \mu_M^2)\,(c\, \mu_T + s_T) - ((2\, \delta\, \eta - \gamma\, \beta\,(N_2 - 2\, N_3))\, s_T + c\, \delta\, \eta\, \mu_T)\, \mu_M\, s_M}{\mu_M\,(c\, \mu_T + s_T)\,((N_3\, \beta - \eta)\, s_M + \delta\, \mu_M)}$$

$Ev_4 < 0$ if $N_1 = 2\, N_3$ and $(N_3^2\, \beta^2 - \eta^2)\, s_M^2 + \delta^2\, \mu_M^2 > 0$. □

At $R_0 = 1$, x_0 for system (3.1) (that is E_0 for model (1.1)) is a non-hyperbolic equilibrium. The local stability of the corresponding equilibrium can not be determined by its linearization matrix $D_x f(x_0, \phi)|_{R_0=1}$. Epidemiologically, this means that only control the basic reproductive number R_0 is not sufficient to completely eliminate infected macrophages and MTb bacteria. Multiple disease outcomes are expected. Therefore, we focus on the situation that $R_0 = 1$, then project three stable manifolds onto the center manifold. Then, dynamical behaviors in system (3.1) near x_0 (that is model (1.1) near E_0) and parameter values around $R_0 = 1$ are governed by the following equation on the center manifold

$$\frac{du}{dt} = a u^2 + b\, u\, \mu + O(u^3), \tag{3.3}$$

where μ denotes the bifurcation parameter, u the center manifold of system (3.1) at $R_0 = 1$. The expression of a and b will be derived in the following. We focus on the simple zero eigenvalue for $D_x f(x_0, \phi)|_{R_0=1}$ and choose the corresponding left and right eigenvectors, v and w, such that $vw = 1$. v and w are written as follows:

$$\begin{gathered} v = \frac{1}{n}\begin{bmatrix} 0 & N_3 + \dfrac{\eta}{\beta} - \dfrac{\delta\, \mu_M}{\beta\, s_M} & 1 & 0 \end{bmatrix},\ w = [w_1,\, w_2,\, w_3,\, w_4]^T, \text{ where,} \\ n = 1 + \frac{(c\, \mu_T + s_T)\,(((N_1 - N_3)\, \beta - \eta)\, s_M + \delta\, \mu_M)\,((N_3\, \beta + \eta)\, s_M - \delta\, \mu_M)}{s_T\, \gamma\, \mu_M\, \beta\, s_M\,(N_1 - N_2)}, \\ w_1 = -\frac{\beta\, s_M}{\mu_M^2},\ w_2 = \frac{(c\, \mu_T + s_T)(((N_1 - N_3)\, \beta - \eta)\, s_M + \delta\, \mu_M)}{s_T\,(N_1 - N_2)\, \gamma\, \mu_M},\ w_3 = 1, \\ w_4 = \frac{(e_B\, s_T + \mu_T)\,(c\, \mu_T + s_T)\,(((N_1 - N_3)\, \beta - \eta)\, s_M + \delta\, \mu_M)\, c_M - s_T\, \mu_M\, \gamma\, c_B\,(N_1 - N_2)\,(e_M\, s_T + \mu_T)}{\gamma\, \mu_M\, \mu_T\,(e_M\, s_T + \mu_T)\,(e_B\, s_T + \mu_T)\,(N_1 - N_2)} \end{gathered} \tag{3.4}$$

Then, we calculate second order partial derivatives of f for $\dfrac{\partial f_i(x_0, \phi)}{\partial x_j \partial x_k}|_{R_0=1}$ and $\dfrac{\partial f_i(x_0, \phi)}{\partial x_j \partial \mu}|_{R_0=1}$. The nonzero elements are presented as follows:

$$\begin{gathered} \frac{\partial f_1(x_0, \phi)}{\partial x_1 \partial x_3}|_{R_0=1} = -\beta,\ \frac{\partial f_2(x_0, \phi)}{\partial x_1 \partial x_3}|_{R_0=1} = \beta,\ \frac{\partial f_3(x_0, \phi)}{\partial x_1 \partial x_3}|_{R_0=1} = -N_3\, \beta - \eta,\ \frac{\partial f_3(x_0, \phi)}{\partial x_3 \partial x_3}|_{R_0=1} = -2\, \frac{\delta}{K}, \\ \frac{\partial f_2(x_0, \phi)}{\partial x_2 \partial x_4}|_{R_0=1} = \frac{\partial f_2(x_0, \phi)}{\partial x_4 \partial x_1}|_{R_0=1} = \frac{\partial f_2(x_0, \phi)}{\partial x_4 \partial x_2}|_{R_0=1} = -\frac{\gamma}{\dfrac{s_T}{\mu_T} + c} + \frac{\gamma\, s_T}{\mu_T\,(\dfrac{s_T}{\mu_T} + c)^2}, \end{gathered}$$

$$\frac{\partial f_3(x_0,\phi)}{\partial x_2 \partial x_4}|_{R_0=1} = \frac{\partial f_3(x_0,\phi)}{\partial x_4 \partial x_1}|_{R_0=1} = \frac{\partial f_3(x_0,\phi)}{\partial x_4 \partial x_2}|_{R_0=1} = \frac{N_2\,\gamma}{\frac{s_T}{\mu_T}+c}\,(1-\frac{s_T}{s_T+\mu_T\,c}),$$
$$\frac{\partial f_4(x_0,\phi)}{\partial x_2 \partial x_4}|_{R_0=1} = \frac{\partial f_4(x_0,\phi)}{\partial x_4 \partial x_1}|_{R_0=1} = \frac{\partial f_4(x_0,\phi)}{\partial x_4 \partial x_2}|_{R_0=1} = \frac{c_M\,\mu_T^2}{(e_M\,s_T+\mu_T)^2},$$
$$\frac{\partial f_3(x_0,\phi)}{\partial x_4 \partial x_4}|_{R_0=1} = \frac{\partial f_4(x_0,\phi)}{\partial x_4 \partial x_3}|_{R_0=1} = \frac{c_B\,\mu_T^2}{(e_B\,s_T+\mu_T)^2},\ \frac{\partial f_2(x_0,\phi)}{\partial x_2 \partial \mu}|_{R_0=1} = -1,\ \frac{\partial f_2(x_0,\phi)}{\partial x_3 \partial \mu}|_{R_0=1} = N_1. \tag{3.5}$$

Applying formulas and results in [7] and [8], we calculate a and b in (3.3) as follows:

$$b \ = \sum_{i,j=1}^{4} v_i\,w_j\,\frac{\partial f_i(x_0,\phi)}{\partial x_j \partial \mu}|_{R_0=1} = \frac{(((N_1-N_3)\,\beta-\eta)\,s_M+\delta\,\mu_M)^2\,(c\,\mu_T+s_T)}{n\,s_T\,\gamma\,\mu_M\,\beta\,s_M\,(N1-N2)} > 0, \text{ if } \quad N_1 > N_2. \tag{3.6}$$

For the conciseness of expression, the parameter a in the center manifold (3.3) is written in terms of parameters, which are statistically significant on the extracellular bacteria load. We apply Latin Hypercube Sampling (LHS) on parameter ranges from experiment in [5], then calculate the partial rank correlation coefficients [9] to show the positive or negative influence that each parameter applied on the extracellular bacteria load. The corresponding p-value smaller than 0.01 is denoted as statistically significant. LHS-PRCC results in Fig. 1 show that b, γ, δ, N_3, and s_M are statistically significant. Further considering the influence on the infection rate β, we have the center manifold coefficient a as follows:

$$\begin{aligned} a = \ & \tfrac{1}{2}\sum_{i,j,k=1}^{4} v_i\,w_j\,w_k\,\frac{\partial f_i(x_0,\phi)}{\partial x_j \partial x_k}|_{R_0=1} \\ = \ & \frac{1}{843183\times 10^8\,\beta\,s_M\,\gamma}(-2125\times 10^{10}\,(\eta+5\,\beta)\,(-25\,\beta+\eta)^2\,s_M^3+375\times 10^6\,(\gamma+\frac{17}{300}\,\delta)\,\delta^2 \\ & +375\times 10^{10}\,(-25\,\beta+\eta)\,((5\,\gamma-\frac{17}{20}\,\delta)\,\beta+\eta\,(\gamma+\frac{17}{100}\,\delta))\,s_M^2 \\ & -75\times 10^9\,\delta\,(-\frac{562122}{5}\,\beta^2\,\gamma+(-\frac{249999718939}{25\times 10^9}\,\gamma-\frac{51}{40}\,\delta)\,\beta+\eta\,(\gamma+\frac{17}{200}\,\delta))\,s_M). \end{aligned} \tag{3.7}$$

Theorem 4. *At $R_0 = 1$, model (1.1) undergoes a transcritical bifurcation, which shows a forward (backward) bifurcation if $a < 0\,(> 0)$.*

4. Bifurcation diagrams and numerical simulations

The Jacobian matrix evaluated at the infected equilibrium $\bar{E}$ yields the characteristic polynomial $P_4 = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$. The corresponding Hurwitz arrangements are $\Delta_1 = a_1$, $\Delta_2 = a_1a_2 - a_3$, $\Delta_3 = (a_1a_2 - a_3)a_3 - a_1^2a_4$, and $\Delta_4 = (a_1a_2 - a_3)a_3a_4 - a_1^2a_4^2$. The infected equilibrium $\bar{E}_1$ undergoes a one-zero eigenvalue bifurcation, iff $a_4 = 0$ and $\Delta_i > 0$ for $i = 1, 2, 3$; a Hopf bifurcation, iff $\Delta_3 = 0$, $\Delta_i > 0$ for $i = 1, 2$, and $a_4 > 0$ [10]. The determined factor to cure MTb infection is the T-cell-mediated immune responses on infected macrophages. In these immune responses, CD 4^+ T cells play an important role by activating cytotoxic T cells and maximizing bactericidal activity of macrophages. The corresponding immune interactions are described by an adaptive immune response term at a rate of γ and the infected cell killing rate b. On the other hand, uncertainty and sensitivity analysis results in Fig. 1 show that γ and b significantly affect MTb bacterium population and are chosen as bifurcation parameters. The sufficient and necessary conditions for one-zero eigenvalue bifurcation provide saddle–node bifurcation, whose bifurcation curve delimits the b-γ parameter plane into three parts: disease clearance or latency region, bistable region, and active disease region in Fig. 2(b). Simulations in Fig. 3 show increasing the infected cells killing rate (b), the disease can progress from latency to oscillation, then to active disease. That is because new bacteria

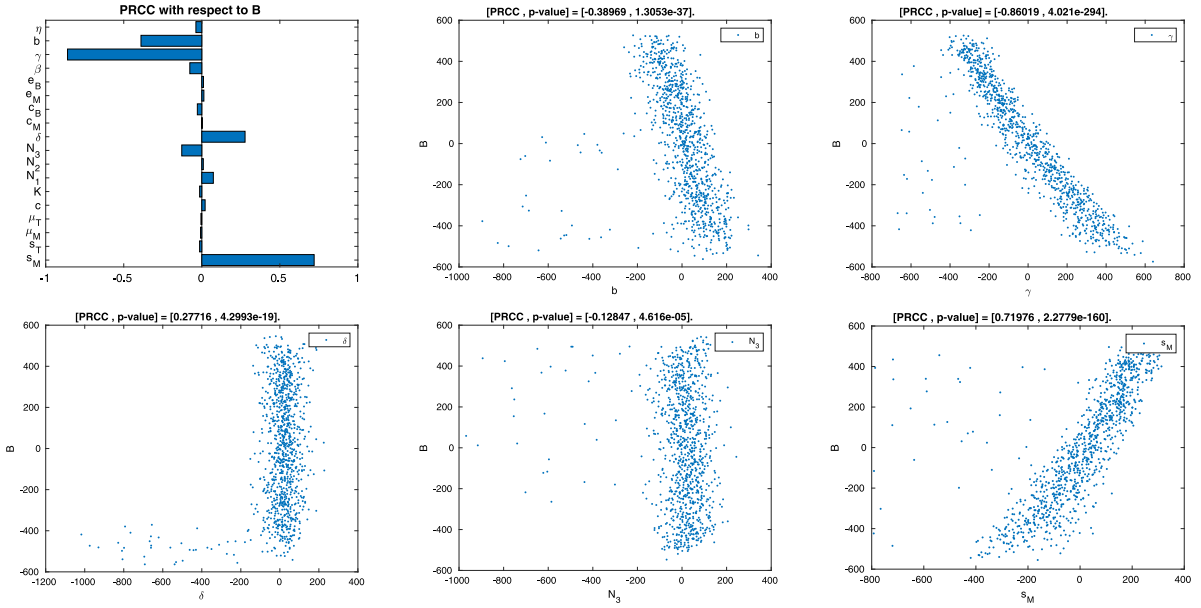

Fig. 1. Sensitivity analysis on all parameter values in their ranges from Table 1 in [5]. Scatter plots are provided for the statistically significant parameters on the extracellular bacteria load.

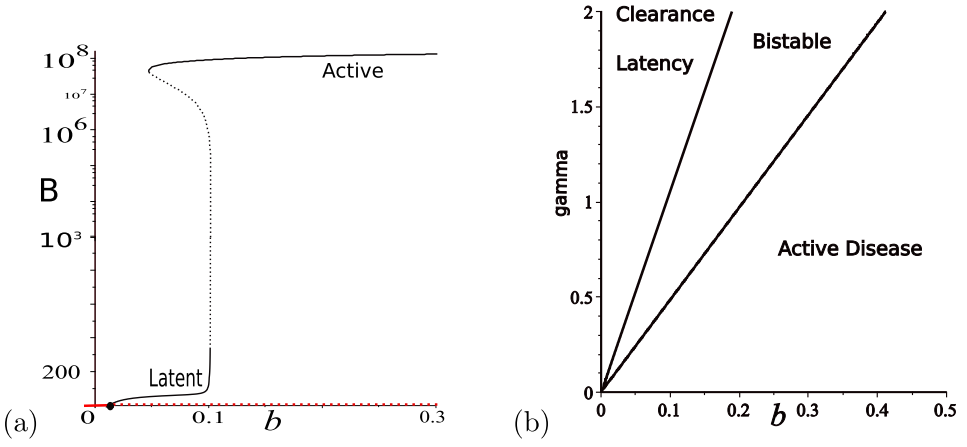

Fig. 2. (a): 1-d bifurcation diagram B (MTb) vs b with $\gamma = 0.5$ and (b): 2-d bifurcation diagram γ vs b for TB model (1.1). Parameter values are taken from [5] as: $s_M = 5000$, $s_T = 6.6$, $\mu_M = 0.01$, $\mu_T = 0.33$, $c = 150$, $K := 1 \times 10^8$, $N_1 = 50$, $N_2 = 20$, $N_3 = 25$, $\delta = 5 \times 10^{-4}$, $c_M = 10^{-3}$, $c_B = 5 \times 10^{-3}$, $e_M = 10^{-4}$, $e_B = 10^{-4}$, $\beta = 2 \times 10^{-7}$, b: bifurcation parameter, $\eta = 1.25 \times 10^{-8}$. (a): Disease free equilibrium and infected equilibriums are in red and black. A Transcritical bifurcation happens at $b = 0.01192$, two Hopf bifurcations at $b = 0.03348$ and $b = 0.08378$, and two saddle–node bifurcations at $b = 0.04665$ and $b = 0.10135$. (b): Two saddle–node bifurcation curves separate the b-γ parameter plane.

can burst out from the death of the infected cells. While Fig. 2 shows that the increase of adaptive immune response rate (γ) can bring the disease to clearance or latency.

5. Conclusion

In this letter, we analyzed a four-dimensional in-host TB model and obtain the analytical formula for the basic reproduction number and the threshold for forward and backward bifurcations. Global sensitivity

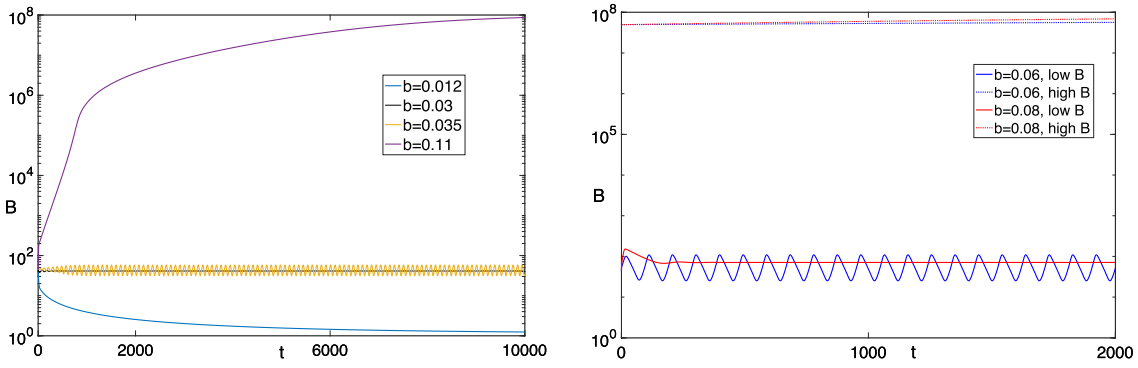

Fig. 3. Simulated bacteria load corresponding to Fig. 2(a). Left figure shows bacteria load stay in low levels at $b = 0.012, 0.03, 0.035$, but grow to high level at $b = 0.11$; right figure shows bistability depending on the initial bacteria load.

analysis on all parameters provide parameters significantly influencing the MTb load, which are the infected macrophages killing rate b, the adaptive immune response rate γ, the bacterium growth rate δ, uninfected macrophages influx rate s_M, and uninfected macrophages engulfment rate N_3. Since the infected macrophages killing rate b, the adaptive immune response rate γ are more related to therapy to eliminate the MTb bacteria. Further bifurcation analysis and simulation shows that the increase of the adaptive immune response rate γ and decrease of the infected macrophages killing rate b can bring down the bacteria load to elimination or latency.

Acknowledgments

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