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ANALYSIS OF SOLUTIONS AND DISEASE PROGRESSIONS FOR A WITHIN-HOST TUBERCULOSIS MODEL

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Abstract. Mycobacterium tuberculosis infection can lead to different disease outcomes, we analyze a within-host tuberculosis infection model considering interactions among macrophages, T lymphocytes, and tuberculosis bacteria to understand the dynamics of disease progression. Four coexisting equilibria that reflect TB disease dynamics are present: clearance, latency, and primary disease, with low and high pathogen loads. We also derive the conditions for backward and forward bifurcations and for global stable disease free equilibrium, which affect how the disease progresses. Numerical bifurcation analysis and simulations elucidate the dynamics of fast and slow disease progression.

1. Introduction

Mycobacterium tuberculosis (Mtb) is a bacterium that causes an ancient and deadly infectious disease in humans, called tuberculosis (TB) [9]. Currently, TB affects approximately one third of the world's population [10, 6]. In 2018, the World Health Organization (WHO) estimated approximately 10 million infections globally, and 1.2 million deaths among HIV-negative people [12]. It has also been found that TB susceptibility and disease are increased in HIV-AIDS infected individuals, resulting in higher mortality rates [8, 1, 14, 16].

The pathological outcomes of TB infection include clearance, latent infection, and primary disease with fast or slow progression [13]. After initial infection, $5-10\%$ of infected subjects can clear the disease. Of the remaining individuals, $5-10\%$ will progress to primary disease, and the rest will remain in a latently infected state with no clinical symptoms, with the possibility of re-activation to primary disease later in their life. A large number of mechanisms have been proposed to explain TB disease progression considering individual factors, including bacterial and immune response mechanisms. However, the most influential factors for TB outcomes are not currently known. Motivated by this, we analyze a TB host-pathogen model first proposed in Ref. [3]. The model incorporates known mechanisms of host-pathogen interaction in TB dynamics, and includes all realistic disease outcomes. Analysis is performed to determine the driving factors behind disease progression and outcome, especially fast or slow progression to primary disease.

The paper is organized as follows. In Section 2, we introduce the established tuberculosis progression model. In Section 3, model dynamics are shown through the proofs of the well-posedness of solutions, the existence of equilibrium solutions, and analyses of the disease free equilibrium. The basic reproduction number R_0 and the vector field on the center manifold for the disease free equilibrium when $R_0 = 1$ are derived analytically. The conditions for the occurrence of the backward and forward bifurcations

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are also derived. In Section 4, numerical continuations are carried out for the infected equilibrium to confirm the existence of a backward bifurcation. The corresponding numerical simulations show the fast and slow disease progressions to latency and primary diseases. Finally, conclusions are drawn in Section 5.

2. Model

The 4-dimensional model (2.1) includes the MTb ideal target cell population, macrophages (their uninfected M_u and infected M_i populations). It also includes the Mtb bacterial population B, and a population of CD4 T cells, which aid in TB clearance. The model is as follows:

$$\begin{aligned}
\frac{dM_u}{dt} &= s_M - \mu_M M_u - \beta M_u B \\
\frac{dM_i}{dt} &= \beta M_u B - bM_i - \gamma M_i \frac{T/M_i}{T/M_i + c} \\
\frac{dB}{dt} &= \delta B\left(1 - \frac{B}{K}\right) + M_i\left(N_1 b + N_2\gamma\frac{T/M_i}{T/M_i + c}\right) - M_u B(\eta + N_3\beta) \\
\frac{dT}{dt} &= s_T + \frac{c_M M_i T}{e_M T + 1} + \frac{c_B B T}{e_B T + 1} - \mu_T T.
\end{aligned} \tag{2.1}$$

Briefly, uninfected macrophages M_u enter the system with constant rate s_M, and can die naturally (μ_M), or be infected by the pathogen B ($\beta M_u B$). It is assumed that infected macrophages can release new bacteria into the system in two different ways: (1) through cell death and bursting b, producing N_1 new bacteria, and (2) through cytotoxic T-lymphocyte killing (represented by the ratio T/M_i) with rate γ and saturating factor c, which releases N_2 new bacteria into the system. It is assumed that the bacteria population can divide ($\delta B(1 - B/K)$ and that bacteria can be lost due to interaction with macrophages. This occurs through immune system neutralization $\eta B M_u$ or macrophage infection $\beta B M_u$ involving, on average, N_3 individual bacteria. Finally, it is assumed that T-cells are produced at a constant rate s_T by the thymus, can be stimulated to proliferate through interactions with the infected macrophage $c_M M_i T/(e_M T + 1)$ and bacteria $c_B BT/(e_B T + 1)$, and can die naturally, with rate μ_T. Infection is initiated with an initial pathogen load. We refer the reader to Du et al. [3] for more detail on the biology and model assumptions. Parameters and their values are listed in Table 1.

In previous work, Du et al. [3] found four biologically realistic equilibria and determined the basic reproduction number. Note that, in the original contribution, there is no mention of the driving factors behind the different outcomes of disease (namely, clearance, latency, and primary disease with fast or slow progression) and only an asymptotic version of the model that neglects the effects of the CD4 T-cell population is used/analyzed. In the following, we expand and elaborate on the four disease outcomes and other interesting aspects of the model using the full model system Eq. 2.1.

3. Model Dynamics

3.1. **Well-posedness of solutions.** Let

$$\mathcal{D} = \left\{(M_u,\, M_i,\, B,\, T) \in \mathbb{R}^4_+ : M_u + M_i \le M_{max},\, B \le B_{max},\, T \le T_{max}\right\}, \quad \text{where}$$

$$\begin{aligned}
M_{max} &= \frac{s_M}{\min\{\mu_M,\, b\}}, \qquad T_{max} = \frac{1}{\mu_T}\left(s_T + \frac{c_M}{e_M}M_{max} + \frac{c_B}{e_B}B_{max}\right), \\
B_{max} &= \frac{K}{2} + \frac{\sqrt{(4K\delta M_{max}(N_1 b + N_2\gamma) + K^2\delta^2}}{2\delta}.
\end{aligned} \tag{3.1}$$

Proposition 3.1. *Under the flow of* (2.1)*, there exists a positive invariant set* $\mathcal{D}$ *that attracts all solutions in* $\mathbb{R}^4_+$ *as time moves forward.*

Proof. The smoothness of the right hand side of model (2.1) guarantees the local existence and uniqueness of the solution of the initial value problem of model (2.1). The trajectories starting from positive initial values never cross the boundary of $\mathbb{R}^4_+$, since

$$\frac{dM_u}{dt}|_{M_u=0} = s_M > 0, \quad \frac{dM_i}{dt}|_{M_i=0} = \beta\, M_u\, B \geq 0,$$

and

$$\frac{dB}{dt}|_{B=0} = M_i\left(N_1 b + N_2\gamma\frac{T}{T+cM_i}\right) \geq 0, \quad \frac{dT}{dt}|_{T=0} = s_T > 0.$$

Next, we show that positive solutions are bounded. Due to the positiveness, we have

$$\frac{d}{dt}(M_u + M_i) < s_M - \mu_M M_u - bM_i \quad \Rightarrow \quad \lim_{t\to+\infty}\sup(M_u + M_i)(t) = \frac{s_M}{\min\{\mu_M,\, b\}} := M_{max}.$$

Moreover,

$$\begin{aligned}
\frac{dB}{dt} < & \quad \delta B\left(1 - \frac{B}{K}\right) + M_i\,(N_1 b + N_2\gamma) - M_u B(\eta + N_3\beta), \quad \tfrac{T}{T+cM_i} \in (0,\, 1) \\
< & \quad -\frac{\delta}{K}B^2 + \delta B + M_{max}\,(N_1 b + N_2\gamma) \\
\Rightarrow & \quad B(t) = K/2 + \tanh\left[\sqrt{(4K\delta M_{max}(N_1 b + N_2\gamma) + K^2\delta^2)}(C_0 + t)/(2K)\right] \\
& \qquad \times\sqrt{(4K\delta M_{max}(N_1 b + N_2\gamma) + K^2\delta^2}/(2\delta),
\end{aligned}$$

where C_0 is determined by initial condition and $C_0 + t > 0$ for sufficiently large t. We have

$$B(t) = \frac{K}{2} + \frac{\sqrt{(4K\delta M_{max}(N_1 b + N_2\gamma) + K^2\delta^2}}{2\delta} := B_{max}.$$

Then, the last equation in (2.1) satisfies

$$\frac{dT}{dt} < s_T + \frac{c_M M_{max} T}{e_M T + 1} + \frac{c_B B_{max} T}{e_B T + 1} - \mu_T T < s_T + \frac{c_M}{e_M}M_{max} + \frac{c_B}{e_B}B_{max} - \mu_T T.$$

It hence follows that

$$T(t) < \frac{1}{\mu_T}\left(s_T + \frac{c_M}{e_M}M_{max} + \frac{c_B}{e_B}B_{max}\right) := T_{max},$$

and the proposition is proven. □

3.2. **Equilibrium Solutions.** Denote model (2.1) as $M_u' = f_1$, $M_i' = f_2$, $B' = f_3$, $T' = f_4$. The corresponding steady states are derived as follows:

$$f_1 = 0; \Rightarrow\ \bar{M}_u(B) = \frac{s_M}{\beta B + \mu_M}. \tag{3.2}$$

Case 1: If $(b+\gamma)M_i - \beta M_u B \neq 0$ or $\beta s_M B - (b+\gamma)(\beta B + \mu_M)M_i \neq 0$, we have

$$\begin{aligned}
& f_2 = 0 \ \Rightarrow\ \bar{T}(\bar{M}_u) = cM_i\left[\frac{\gamma M_i}{(b+\gamma)M_i - \beta\bar{M}_u B} - 1\right] \overset{(3.2)}{\Longrightarrow} \\
& \bar{T}(B) = \frac{[\beta s_M B - (\beta B + \mu_M)bM_i]cM_i}{\beta s_M B - (b+\gamma)(\beta B + \mu_M)M_i}, \qquad (3.3) \\
& \bar{T}(B) > 0 \quad \text{if} \quad \beta s_M B < (\beta B + \mu_M)bM_i \quad \text{or} \quad \beta s_M B > (b+\gamma)(\beta B + \mu_M)M_i.
\end{aligned}$$

Considering the preceding results (3.2) and (3.3), we obtain

$$f_3 = c\gamma M_i^2 f_{3a} f_{3b} = 0, \quad \text{where}$$

$$f_{3a} = (b+\gamma)(\beta B + \mu_M) M_i - \beta s_M B$$

$$f_{3b} = Kb\,(\beta B + \mu_M)\, M_i + ((\beta B + \mu_M)\delta + s_M[(N2 - N3)\beta - \eta])KB - B^2\delta(\beta B + \mu_M).$$

The existence of $\bar{T}$ in (3.3) implies $f_{3a} \neq 0$. Further, $M_i = 0$ induces that $f_4(M_u = \bar{M}_u(B),\, M_i = 0,\, B,\, \bar{T}(B) = 0) = s_T \neq 0$. This indicates that the equilibrium does not exist. Therefore $f_3 = 0$ only implies $f_{3b} = 0$ followed by

$$\begin{aligned} &\bar{M}_i(B) = \left(\frac{B\delta}{K} - \frac{\delta + s_M(N_2 - N_3)\beta - s_M\eta}{\beta B + \mu_M}\right)\frac{B}{b(N1 - N2)}, \\ &\bar{M}_i(B) > 0 \quad \text{if} \quad \frac{B\delta}{K} > \frac{\delta + s_M(N_2 - N_3)\beta - s_M\eta}{\beta B + \mu_M} \quad \text{and} \quad N_1 > N_2. \end{aligned} \tag{3.4}$$

The B in (3.4) satisfies $f_4(\bar{M}_u(B),\, \bar{M}_i(B),\, B,\, \bar{T}(B)) = 0$, the following is true:

$$\begin{aligned} F(B) = &-e_B e_M \mu_T \bar{T}^3(B) + \left[(c_M \bar{M}_i(B) + e_M s_T - \mu_T)e_B + e_M(c_B B - \mu_T)\right)\bar{T}^2(B) \\ &+ \left[c_B B + c_M \bar{M}_i(B) + e_B s_T + e_M s_T - \mu_T\right]\bar{T}(B) + s_T = 0. \end{aligned} \tag{3.5}$$

Then, we find the infected equilibrium $E^* = (\bar{M}_u(B),\, \bar{M}_i(B),\, B,\, \bar{T}(B))$. We note that there could be more than one solution, and up to three feasible infected equilibria.
Case 2: If $\beta s_M B - (b+\gamma)(\beta B + \mu_M)M_i = 0$, we have

$$f_2 = 0 \;\Rightarrow\; \bar{M}_{i0} = \frac{\beta s_M B}{(b+\gamma)(\beta B + \mu_M)}. \tag{3.6}$$

Then substituting $\bar{M}_u(B)$ in (3.2) and $\bar{M}_{i0}$ in (3.6) into $f_3(\bar{M}_u(B),\, \bar{M}_{i0}) = 0$, yields

$$\bar{B}_0 = 0. \tag{3.7}$$

This is followed by $f_4(\bar{M}_u(B),\, \bar{M}_{i0},\, \bar{B}_0) = 0$, which yields

$$\bar{T}_0 = \frac{s_T}{\mu_T}. \tag{3.8}$$

We thus find the disease free equilibrium (DFE) $E_0 = (\bar{M}_u(\bar{B}_0),\, \bar{M}_{i0}(\bar{B}_0),\, \bar{B}_0,\, \bar{T}_0)$, where $\bar{M}_u(\bar{B}_0) = s_M/\mu_M$ and $\bar{M}_{i0}(\bar{B}_0) = 0$.

3.3. **Analysis of the disease free equilibrium.**

3.3.1. *Calculation of the basic reproduction number.* Following the next-generation matrix approach in Ref. [11], the basic reproduction number R_0 is the spectral radius of FV^{-1}, where

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\beta s_M}{\mu_M} \\ N_1 b + N_2\gamma & \delta \end{bmatrix}\begin{bmatrix} b+\gamma & 0 \\ 0 & \frac{s_M}{\mu_M}(N_3\beta + \eta) \end{bmatrix}^{-1} = \begin{bmatrix} 0 & \frac{\beta}{N_3\beta + \eta} \\ \frac{N_1 b + N_2\gamma}{b+\gamma} & \frac{\mu_M\delta}{s_M(N_3\beta + \eta)} \end{bmatrix},$$

and

$$R_0 = \rho(FV^{-1}) = \frac{\delta\mu_M}{2s_M(N_3\beta + \eta)} + \frac{1}{2}\left[\frac{\delta^2\mu_M^2}{s_M^2(N_3\beta + \eta)^2} + \frac{4\beta(N_1 b + N_2\gamma)}{(N_3\beta + \eta)(b+\gamma)}\right]^{1/2}. \tag{3.9}$$

The Jacobian matrix of model (2.1) at the disease free equilibrium is:

$$J_0 = \begin{bmatrix} -\mu_M & 0 & -\frac{\beta s_M}{\mu_M} & 0 \\ 0 & -b-\gamma & \frac{\beta s_M}{\mu_M} & 0 \\ 0 & N_1 b + N_2\gamma & \delta - \frac{s_M}{\mu_M}(N_3\beta+\eta) & 0 \\ 0 & \frac{c_M s_T}{e_M s_T + \mu_T} & \frac{c_B s_T}{e_B s_T + \mu_T} & -\mu_T \end{bmatrix}, \tag{3.10}$$

and gives the following characteristic equation

$$(z+\mu_T)(z+\mu_M)\left(z^2+Pz+Q\right)=0, \tag{3.11}$$

where

$$P = b+\gamma-\delta+\frac{s_M}{\mu_M}(N_3\beta+\eta),$$
$$Q = \left[(-N_2+N_3)\gamma\beta - b(N_1-N_3)\beta + \eta(b+\gamma)\right]\frac{s_M}{\mu_M} - \delta(b+\gamma).$$

Equation (3.11) admits at least two negative roots, $z=-\mu_T$ and $z=-\mu_M$. The third root, $z=\delta-b-\gamma-\frac{s_M}{\mu_M}(N_3\beta+\eta)$, is negative if $b+\gamma+\frac{s_M}{\mu_M}(N_3\beta+\eta)>\delta$. The last root is zero, if

$$\left[(-N_2+N_3)\gamma\beta - b(N_1-N_3)\beta + \eta(b+\gamma)\right]\frac{s_M}{\mu_M} - \delta(b+\gamma) = 0, \tag{3.12}$$

which is equivalent to $R_0=1$.

Theorem 3.1. *Under the condition $b+\gamma+\frac{s_M}{\mu_M}(N_3\beta+\eta)>\delta$, the disease free equilibrium E_0 is locally asymptotically stable if $R_0<1$ and unstable if $R_0>1$.*

3.3.2. *Existence of a backward bifurcation.* Following Theorem 4.1 in Ref. [2], we first shift the disease free equilibrium to the origin by letting $x_1=M_u-\frac{s_M}{\mu_M}$, $x_2=M_i-0$, $x_3=B-0$, $x_4=T-\frac{s_T}{\mu_T}$, and $\phi=\beta-\beta_T$. Here $R_0(\beta_T)=1$ and

$$\beta_T = \frac{(-\delta\mu_M+\eta s_M)(b+\gamma)}{s_M\gamma(N_2-N_3)\gamma + s_M b(N_1-N_3)}.$$

Then we compute the approximated center manifold for the system near the origin with one simple zero eigenvalue at $R_0=1$, and three negative eigenvalues. We choose a right eigenvector associated with the simple zero eigenvalue, w, and the left eigenvector, v, satisfying $vw=1$ as follows:

$$w = \frac{1}{n}\begin{bmatrix} \frac{(\delta\mu_M-\eta s_M)(b+\gamma)}{\mu_M^2\tilde{w}} \\ \frac{\delta\mu_M-\eta s_M}{\mu_M\tilde{w}} \\ 1 \\ \frac{s_T\left\{\left[(\tilde{w}c_B-\delta c_M)\mu_T + (e_M\tilde{w}c_B-\delta c_M e_B)s_T\right]\mu_M + \eta c_M s_M(e_B s_T+\mu_T)\right\}}{(e_B s_T+\mu_T)(e_M s_T+\mu_T)\mu_M\mu_T\tilde{w}} \end{bmatrix},$$

$$v = \begin{bmatrix} 0, & \frac{N_1 b+N_2\gamma}{b+\gamma}, & 1, & 0 \end{bmatrix},$$

where

$$n = \frac{(N_2 - N_3)\mu_M\gamma + [(N_1 + N_2 - 2N_3)b - N_2\delta]\mu_M\gamma + N_2 s_M\eta\gamma}{\mu_M(b+\gamma)\tilde{w}} + \frac{(N_1 - N_3)b^2\mu_M - N_1\delta b\mu_M + N_1 s_M\eta b}{\mu_M(b+\gamma)\tilde{w}}$$

and

$$\tilde{w} = (N_2 - N_3)\gamma + b(N_1 - N_3).$$

Further, the flow of the center manifold $y(t)$ truncated at the quadratic term is written as

$$\dot{y} = \mathcal{A}y^2 + \mathcal{B}\phi y, \tag{3.13}$$

$$\mathcal{A} = \frac{v}{2}\left[w'\left(\frac{\partial f_1}{\partial x_i \partial x_j}\right)\Big|_{E_0} w,\ w'\left(\frac{\partial f_2}{\partial x_i \partial x_j}\right)\Big|_{E_0} w,\ w'\left(\frac{\partial f_3}{\partial x_i \partial x_j}\right)\Big|_{E_0} w,\ w'\left(\frac{\partial f_4}{\partial x_i \partial x_j}\right)\Big|_{E_0} w\right]'$$

$$= \frac{A_n}{A_d},$$

$$A_n = ((\tilde{A} - [\mu_T c s_M(N_1 - N_2)]b\gamma)K\delta - s_M[(N_2 - N_3)\gamma + b(N_1 - N_3)]^2(b+\gamma)s_T)\mu_M^2\delta,$$

$$- s_M\delta K\eta\mu_M\tilde{A} + K\mu_T\gamma bcs_M^3\eta^2(N_1 - N_2),$$

$$\tilde{A} = -s_T(N_2 - N_3)\gamma^3 - bs_T(N_1 + 2N_2 - 3N_3)\gamma^2 - b^3 s_T(N_1 - N_3)$$

$$- (2N_1 + N_2 - 3N_3)s_T b^2\gamma + 2(N1 - N2)\mu_T c s_M b\gamma,$$

$$A_d = s_M\mu_M^2[(N_2 - N_3)\gamma + b(N_1 - N_3)]^2(b+\gamma)s_T K,$$

and

$$\mathcal{B} = v\left(\frac{\partial f_i}{\partial x_i \partial \beta}\right)_{E_0} w = \frac{[(N_2 - N_3)\gamma + b(N_1 - N_3)]s_M}{(b+\gamma)\mu_M},$$

where i, $j = 1 \ldots 4$. The non-zero terms in $\left(\frac{\partial f_k}{\partial x_i \partial x_j}\right)\Big|_{E_0}$, where i, j, $k = 1 \ldots 4$, are

$$\frac{\partial f_1}{\partial x_1 \partial x_3}\Big|_{E_0} = \frac{\partial f_1}{\partial x_3 \partial x_1}\Big|_{E_0} = -\frac{\partial f_2}{\partial x_1 \partial x_3}\Big|_{E_0} = -\frac{\partial f_2}{\partial x_3 \partial x_1}\Big|_{E_0} = \frac{(\delta\mu_M - \eta s_M)(b+\gamma)}{[(N_2 - N_3)\gamma + b(N_1 - N_3)]s_M},$$

$$\frac{\partial f_3}{\partial x_1 \partial x_3}\Big|_{E_0} = \frac{\partial f_3}{\partial x_3 \partial x_1}\Big|_{E_0} = N_3\frac{\partial f_1}{\partial x_1 \partial x_3}\Big|_{E_0} - \eta,$$

$$\frac{\partial f_2}{\partial x_2 \partial x_2}\Big|_{E_0} = \frac{2\gamma\mu_T c}{s_T}, \quad \frac{\partial f_3}{\partial x_2 \partial x_2}\Big|_{E_0} = -N_2\frac{2\gamma\mu_T c}{s_T}, \quad \frac{\partial f_3}{\partial x_3 \partial x_3}\Big|_{E_0} = -2\frac{\delta}{K},$$

$$\frac{\partial f_4}{\partial x_2 \partial x_4}\Big|_{E_0} = \frac{\partial f_4}{\partial x_4 \partial x_2}\Big|_{E_0} = \frac{c_M\mu_T^2}{(e_M s_T + \mu_T)^2}, \quad \frac{\partial f_4}{\partial x_3 \partial x_4}\Big|_{E_0} = \frac{\partial f_4}{\partial x_4 \partial x_3}\Big|_{E_0} = \frac{c_B\mu_T^2}{(e_B s_T + \mu_T)^2}.$$

Theorem 3.2. *Under the condition $\mathcal{B} > 0$, we have $A_d > 0$. Then the model (2.1) at the disease free equilibrium E_0, when $R_0 = 1$ undergoes (1) a backward bifurcation if $A_n > 0$ and (2) a forward bifurcation if $A_n < 0$. Furthermore, $A_n(c = 0, \beta = \beta_T, b = b_b) = 0$, where*

$$b_b = \gamma \frac{[(N_2 - N_3)s_M + K\delta]\mu_M - \eta K s_M}{[(N_3 - N_1)s_M - K\delta]\mu_M + \eta K s_M}. \tag{3.14}$$

3.3.3. *Global stability analysis for the disease free equilibrium E_0.* Proposition 3.1 shows that state variables M_u, M_i, B, and T are bounded for sufficiently large time. That is, there exists a time $T > 0$ such that $M_u < M_{max}$, $M_i < M_{max}$, $B < B_{max}$, and $T < T_{max}$. Applying the "fluctuation lemma" [5], there exists time sequences $\tau_n \to \infty$ and $\sigma_n \to +\infty$ such that

$$\begin{aligned} M_i^\infty &:= \limsup_{t\to\infty} M_i(t) = \lim_{n\to+\infty} M_i(\tau_n) \quad \text{and } \lim_{n\to+\infty} \frac{dM_i(\tau_n)}{dt} = 0, \\ B^\infty &:= \limsup_{t\to\infty} B(t) = \lim_{n\to+\infty} B(\sigma_n) \quad \text{and } \lim_{n\to+\infty} \frac{dB(\sigma_n)}{dt} = 0. \end{aligned} \tag{3.15}$$

The preceding equations are followed by

$$\begin{aligned} &\beta M_u(\tau_n)B(\tau_n) - bM_i^\infty - \gamma M_i^\infty \frac{T(\tau_n)}{T(\tau_n) + cM_i^\infty} = 0 \\ \Longrightarrow\ &\beta M_u(\tau_n)B(\tau_n) = \left(b + \gamma \frac{T(\tau_n)}{T(\tau_n) + cM_i^\infty}\right) M_i^\infty \le \beta M_{max} B^\infty \\ \longrightarrow\ &M_i^\infty \le \frac{\beta M_{max} B^\infty}{b + \gamma \dfrac{T(\tau_n)}{T(\tau_n) + cM_i^\infty}} < \frac{\beta}{b} M_{max} B^\infty, \end{aligned} \tag{3.16}$$

and

$$\begin{aligned} &\delta B^\infty \left(1 - \tfrac{B^\infty}{K}\right) + M_i(\sigma_n)\left(N_1 b + N_2 \gamma \tfrac{T(\sigma_n)}{T(\sigma_n)+cM_i}\right) - M_u(\sigma_n)B^\infty(\eta + N_3\beta) = 0 \implies \\ &-\delta B^\infty \left(1 - \tfrac{B^\infty}{K}\right) + M_u(\sigma_n)B^\infty(\eta + N_3\beta) = M_i(\sigma_n)\left(N_1 b + N_2 \gamma \tfrac{T(\sigma_n)}{T(\sigma_n)+cM_i}\right) \le M_i(\sigma_n)\left(N_1 b + N_2\gamma\right) \\ &\Longrightarrow \left[M_u(\sigma_n)(\eta + N_3\beta) - \delta\right] B^\infty \le M_i(\sigma_n)\left(N_1 b + N_2\gamma\right) \implies \\ &B^\infty \le M_i(\sigma_n) \frac{N_1 b + N_2\gamma}{M_u(\sigma_n)(\eta + N_3\beta) - \delta} \le \frac{N_1 b + N_2\gamma}{M_u(\sigma_n)(\eta + N_3\beta) - \delta} M_i^\infty, \end{aligned} \tag{3.17}$$

where $\frac{T(\tau_n)}{T(\tau_n)+cM_i^\infty} \le 1$. Subsequently,

$$M_i^\infty \le \frac{\beta}{b} M_{max} B^\infty \le \frac{\beta}{b} M_{max} \frac{N_1 b + N_2\gamma}{M_u(\sigma_n)(\eta + N_3\beta) - \delta} M_i^\infty. \tag{3.18}$$

If

$$\frac{\beta}{b} M_{max} \frac{N_1 b + N_2\gamma}{M_u(\sigma_n)(\eta + N_3\beta) - \delta} \le 1,$$

or equivalently

$$M_u(\sigma_n) \ge \frac{1}{\eta + N_3\beta}\left[\frac{\beta s_M}{b\mu_M}(N_1 b + N_2\gamma) + \delta\right] := M_u^{max}, \tag{3.19}$$

then $M_i^\infty = 0$, implying $B^\infty = 0$, and the disease free equilibrium E_0 is globally stable.

Theorem 3.3. *If $b + \gamma + \frac{s_M}{\mu_M}(N_3\beta + \eta) > \delta$ and $R_0 < 1$, the uninfected macrophage population M_u should satisfy $M_u \ge M_u^{max}$ to completely eliminate TB infection.*

Symbol	Description (Unites)	Value (Range)	Source
s_M	recruitment rate of M_u (1/ml day)	5000 (0.33, 33)	[13] [7] [4]
s_T	recruitment rate of T (1/ml day)	6.6 (3300, 7000)	[13] [7] [4]
μ_M	death rate of M_u (1/day)	0.01 (0.01, 0.011)	[13] [7] [4]
b	loss rate of M_i (1/day)	0.11 (0.05, 0.5)	[13] [7] [4]
μ_T	death rate of T (1/day)	0.33 (0.05, 0.33)	[13] [7] [4]
β	infection rate by B (1/day)	2×10^{-7} (10^{-8}, 10^{-5})	[13] [7] [4]
η	bacteria killing rate by M_u rate (1/ml day)	1.25×10^{-8} (1.25×10^{-9}, 1.25×10^{-7})	[13] [7] [4]
γ	cell-mediated immunity rate (1/day)	0.5 (0.1, 2)	[13] [7] [4]
δ	proliferation rate of B (1/day)	5×10^{-4} (0, 0.26)	[13] [7] [4]
c_M	expansion rate of T induce by M_i (1/day)	10^{-3} (10^{-8}, 1)	Estimated
c_B	expansion rate of T induce by B (1/day)	5×10^{-3} (10^{-8}, 1)	Estimated
e_M	saturating factor of T expansion related to M_i	10^{-4} (10^{-6}, 10^{-2})	Estimated
e_B	saturating factor of T expansion related to B	10^{-4} (10^{-6}, 10^{-2})	Estimated
c	half-saturation ratio for M_i lysis (T/M_i)	3 (0.3, 30)	Estimated
K	carrying capacity of B (1/ml)	10^{-8} (10^{6}, 10^{10})	Estimated
N_1	max MOI of M_i (B/M_i)	50 (50, 100)	[13] [7] [4]
N_2	max No. of B released by apoptosis (T/M_i)	20 (20, 30)	[13] [7] [4]
N_3	$N_3 = N_1/2$ (B/M_i)	25 (25, 50)	[13] [7] [4]
M_u	uninfected macrophages		
M_i	infected macrophages		
B	extra and intra-cellular bacteria		
T	CD4 T-cells		

TABLE 1. Parameter Symbol, Descriptions, Values, and Sources [3]

The occurrence of a backward bifurcation destabilizes the globally stable disease free equilibrium E_0 under the condition $R_0 < 1$ and an extra condition to regain stability is needed, i.e. $b + \gamma + \frac{s_M}{\mu_M}(N_3\beta + \eta) > \delta$, as shown in Theorem 3.3. In the next section, we verify the existence of a backward bifurcation computationally and investigate the associated dynamical behaviors by numerical simulations.

4. Bifurcation analysis and numerical simulations

Consider the n-dimensional nonlinear system with m parameter values

$$\frac{dx}{dt} = f(x, p), \quad x \in R^n, \quad p \in R^m, \quad f : R^{n+m} \to R^n. \tag{4.1}$$

The equilibrium solutions $x_e = x_e(p)$ are derived from the equilibrium condition

$$f(x_e(p), p) = 0, \quad x \in R^n, \quad p \in R^m. \tag{4.2}$$

The local stability of the equilibrium points $x_e(p)$ is determined by the eigenvalues of the Jacobian $J(p) = [\partial f_i(x_e(p), p)/\partial x_j]$, which are the roots of the corresponding characteristic polynomial equation

$$P_n(\lambda) = \det[\lambda I - J(p)] = \lambda + a_1(p)\lambda^{n-1} + a_2(p)\lambda^{n-2} + \cdots + a_{n-1}(p)\lambda + a_n(p). \tag{4.3}$$

The necessary and sufficient conditions for zero-eigenvalue bifurcation (zero-singularity) are given in Ref. [15].

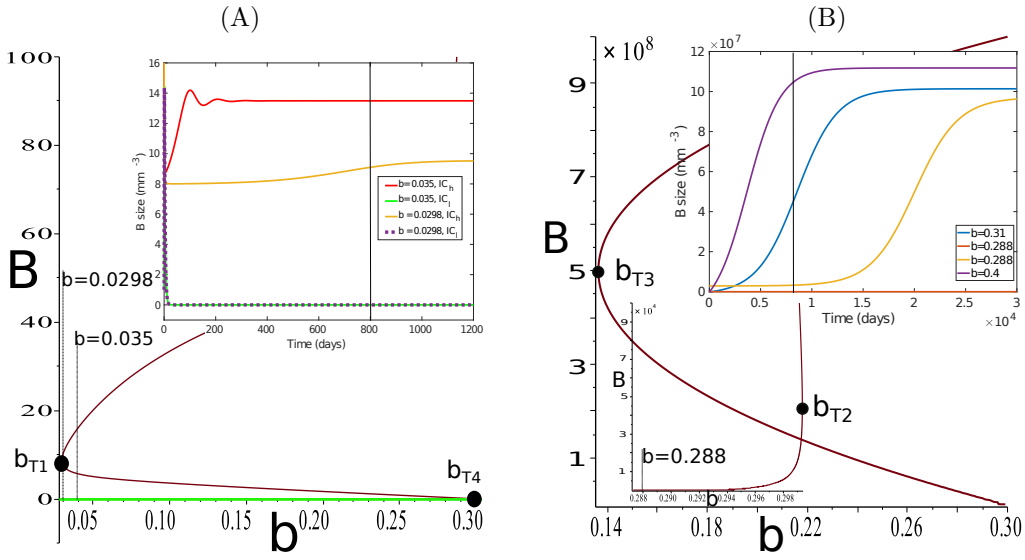

FIGURE 1. Bifurcation diagrams of model (2.1) with B vs b and simulations. E_0 and E_1 are in green and red curves. Four zero-eigenvalue bifurcation are denoted as black points as b_{T1}, b_{T2}, b_{T3}, and b_{T4}. Simulations are carried out for five fixed b values as $b = 0.0298$, $b = 0.035$, $b = 0.288$, $b = 0.31$, and $b = 0.4$. The first three b values shows bistability. The last three b values show different progression speed for the bacterial population B.

Theorem 4.1. *The necessary and sufficient conditions for system* (4.1) *to have a k-zero singularity at a fixed point (equilibrium), $x = x_e(p)$, of the system are given by*

$$a_n(p) = a_{n-1}(p) = \cdots = a_{n+1-k}(p) = 0, \tag{4.4}$$

which $a_i(p)$'s are the coefficients of the characteristic polynomial (4.3)*. Further, if the remaining coefficients a_1, a_2, ... a_{n-k} still obey the Hurwitz conditions for order $n - k$, then all the remaining eigenvalues of the Jacobian have negative real parts.*

Based on the results of the uncertainty and sensitivity analysis in Ref. [3], the model is significantly affected by the change of macrophage loss rate b, the infection rate β, cell-mediated immunity rate γ, and bacterial killing rate η. We thus choose the macrophage loss rate b as a bifurcation parameter to verify the analytical result for the backward bifurcation discussed in Theorem 3.1. The other parameter values are fixed and shown in Table 1.

Using Theorem 4.1, we numerically find four zero-eigenvalue bifurcation critical points at $b_{T1} = 0.0295$, with $E_{T1} = (497833, 122, 8.7, 40)$, $b_{T2} = 0.2993$, with $E_{T2} = (21089, 2664, 45417, 6952168)$, $b_{T3} = 0.1363$, with $E_{T3} = (20, 3055, 49998972, 7575684467)$, and $b_{T4} = 0.3000036$, which yields $E_{T4} = (500000, 0, 0, 20)$. The summarized bifurcation, equilibria, and their stability are shown in Figure 1. Two values, i.e. $b = 0.0298$, $b = 0.035$, are chosen near b_{T1} and time series show that bistability occur for both b values, with solutions landing onto different equilibria depending on their initial conditions (see panel (A)). This is of interest because it means that the disease can die out or persist to latency depending on the initial infection status. Interestingly, the progression to latency shows different dynamics and lasts different periods of time for the chosen b values. The red and yellow curves take different time to stabilize at their latency levels.

We then take three b values, i.e. $b = 0.288$, $b = 0.31$, and $b = 0.4$, close to b_{T2} (see panel (B)). Again, bistability occurs when $b = 0.288$ on the left of b_{T2}. There is an obvious difference in the speed of disease progression for the three different b values, as shown by the curves in the inset of Figure 1(B). These examples of fast and slow disease progression dynamics seem to confirm the numerical findings in Ref. [3] and are the object of current investigation.

5. Conclusion

In this paper, we analyze a four-dimensional within-host model (2.1) for tuberculosis infection, which has been previously proposed and studied numerically in Ref. [3].

We carry out analyses for the well-posedness and boundedness for solutions, existence of the disease free and infected equilibriums and local and global stability analysis. A bifurcation analysis for the disease free equilibrium is also conducted, and a numerical continuation for the infected equilibrium shows when a backward bifurcation occurs. Numerical simulations finally show how fast and slow disease progressions take place close to the bifurcation, with examples of bistability behaviour. This is important because different initial infections can lead to different disease progressions, with considerable differences among latency times.

An in-depth analysis of the bifurcation scenario of this model is currently under progress, with the aim of characterising the different, possible behaviours towards infection that TB shows.

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