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ANALYSIS OF A SIMPLE MATHEMATICAL MODEL ON TUBERCULOUS GRANULOMA*

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Abstract. This paper discusses a mathematical model describing the formation of tuberculosis(TB) granulomas. The main purpose is to analyze the change trend of Mtb and immune cells in different stages after Mtb invaded the host. The theoretical analysis indicates that the existence of bacteria-free equilibrium and bacteria-present equilibrium, and that they are globally stable under different conditions. In addition, the sensitivity analysis is performed on the parameters, which determines the parameters that have the greatest impact on Mtb invading the host. The stage of no infection, the latent TB infection(LTBIs) and active TB corresponding to the clearance, survival or growth and reproduction of Mtb are displayed by the numerical simulations. The results suggest that whether the individuals infected with Mtb will be progressed to the active TB depends on the immune system of individuals.

1. Introduction

The classic pathological feature of TB is that the host forms TB granuloma in the lung in the process of fighting against the invasion of Mtb [1]. TB granuloma is mainly composed of Mtb, macrophages, immune T cells and other immune cells, and it is the environment in which Mtb continues to grow or survive, and is also the battlefield where immune cells kill Mtb [2]. If TB granuloma can maintain a balance in the immune response, provide enough immune cell activation to inhibit bacterial growth and regulate inflammation, the infected individuals will be in a state of LTBIs. If TB granuloma cannot keep balance in the immune response, resulting in rapid growth of the number of bacteria, the LTBIs will develop into an active TB patients [3].

The immune response after Mtb infection is a very complex process, and the simple experimental medical research has certain limitations. The combination of experimental medical research and mathematical models will help to better understand the complex internal causes of Mtb transmission and provide a reasonable explanation for the observed phenomenon. Therefore, it has led to many papers using mathematical models to explore the complex immune process [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. Mathematical models used include ordinary differential equation models [4, 5, 6, 7, 8, 9], partial differential equation models [10, 11, 12, 13], agent based models [14, 15], and mixed multi-scale models [16].

The ordinary differential equation model is reasonable without considering the spatial factors of TB granuloma. Here, we will also establish an ordinary differential equation model to describe the immune response after Mtb infection. For this reason, we assume that

(i) Macrophages in the host will automatically activate to fight against the invasion of Mtb, regardless of static macrophages.

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(ii) After being engulfed by macrophages, Mtb may be eliminated, or it may live or even grow and reproduce in macrophages, which means that intracellular Mtb can be characterized by infected macrophages.

(iii) Due to the fact that clinical and epidemiological tests for TB do not divided bacteria in internal and external, we will consider only one population of bacteria as in [17].

(iv) We ignore the role of cytokines because of the complexity of their role in the immune response.

Based on the above assumptions and [17, 18], we will mainly discuss the role of activated infected macrophages, infected macrophages, extracellular Mtb and immune T cells, and use $M_U(t)$, $M_I(t)$, $B(t)$, and $T(t)$ to represent the population level of activated infected macrophages, infected macrophages, Mtb, and immune T cells at t time, respectively. Then, a simple mathematical model describing tuberculous granuloma is as follows:

$$\begin{cases} \dfrac{dM_U}{dt} = \Lambda_U - \mu_U M_U - \beta B M_U, \\ \dfrac{dM_I}{dt} = \beta B M_U - \alpha_T M_I T - \mu_I M_I, \\ \dfrac{dB}{dt} = r\mu_I M_I - \gamma_U M_U B - \mu_B B, \\ \dfrac{dT}{dt} = \Lambda_T + \sigma_M M_I T - \mu_T T, \end{cases} \tag{1.1}$$

with the initial condition

$$M_U(0) = M_U^0 \geq 0,\ M_I(0) = M_I^0 \geq 0,\ B(0) = B^0 \geq 0,\ T(0) = T^0 \geq 0. \tag{1.2}$$

Here, Λ_U represents the constant replenishment rate of activated infected macrophages, μ_U represents the mortality rate of activated infected macrophages, β represents the incidence of activated infected macrophages becoming infected macrophages, μ_I represents the mortality rate of infected macrophages, α_T represents the clearance rate of immune T cells clearing infected macrophages, r represents the average number of bacteria produced inside an infected macrophage, γ_U represents the phagocytosis rate of activated infected macrophages to Mtb, μ_B represents the mortality rate of Mtb, Λ_T represents the natural recruitment of immune T cells, σ_M represents the activation rate of immune T cells by infected macrophages, and μ_T represents the mortality rate of T cells.

Our interest in this paper is to study the dynamic behavior of mathematical models describing the formation of TB granulomas. This paper is organized as follows. In section 2, the well-posedness of the system (1.1) are given. In section 3, the model analysis reveals the existence of equilibria, especially the existence and uniqueness of bacteria-present equilibrium. In section 4, the global stability of bacteria-free equilibrium and bacteria-present equilibrium is proved under some conditions. In section 5, a sensitivity analysis is performed on the parameters, and the different infection states of Mtb entering the host are numerically simulated. Finally, we give discussion and conclusions.

2. **Preliminaries and well-posedness**

In this section, we will investigate the non-negativity and ultimately boundedness of the solutions of model (1.1) with non-negative initial condition.

Theorem 2.1. *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*

$$\Gamma = \left\{ (M_U, M_I, B, T) \in \mathbb{R}^4_+ | M_U(t) + M_I(t) \leq \mathcal{M}, B(t) \leq \mathcal{B}, T(t) \leq \frac{\Lambda_T}{\mu_T - \sigma_M \mathcal{M}} \right\}.$$

where

$$\mathcal{M} = \frac{\Lambda_U}{\min\{\mu_U, \mu_I\}}$$

and $\mathcal{B}$ is a bounded positive constant.

Proof. We first prove that $M_U(t) \geq 0$ for $t \geq 0$. The first equation of model (1.1) implies that

$$M_U(t) = e^{-\int_0^t \left(\mu_U + \beta B(s)\right) ds} \left(M_U^0 + \Lambda_U \int_0^t e^{\int_0^s \left(\mu_U + \beta B(m)\right) dm} ds\right) > 0.$$

It means that $M_U(t) > 0$ for any $t \geq 0$. Similarly, by using of the fourth equation of model (1.1), we have

$$T(t) = e^{\int_0^t \left(\sigma_M M_I(s) - \mu_T\right) ds} \left(T^0 + \Lambda_T \int_0^t e^{-\int_0^s \left(\sigma_M M_I(m) - \mu_T\right) dm} ds\right) > 0.$$

That is, $T(t) > 0$ for any $t \geq 0$.

Secondly, for any nonnegative initial value $M_I^0 \geq 0$ and $B^0 \geq 0$, we prove that $M_I(t) \geq 0$, and $B(t) \geq 0$ for $t \geq 0$. We assert that the conclusion is valid, otherwise, when $M_I^0 > 0$ and $B^0 > 0$, the continuous dependence of solutions on initial values implies there exists $t_1 > 0$, $t_2 > 0$, such that $M_I(t_1) = 0$, $M_I(t) > 0$ for $t \in [0, t_1)$, $M_I'(t_1) < 0$, and $B(t_2) = 0$, $B(t) > 0$ for $t \in [0, t_2)$, $B'(t_2) < 0$. Without loss of generality, we assume that $t_1 = \min\{t_1, t_2\}$, then $M_I(t_1) = 0$, $B(t_1) > 0$, $M_I(t) > 0$, and $B(t) > 0$ for $t \in [0, t_1)$. The second equation of model (1.1) implies that

$$\frac{dM_I(t)}{dt} \mid_{t=t_1} = \beta B(t_1) M_U(t_1) > 0,$$

that is, $M'(t_1) > 0$. Similarly, when $t_2 = \min\{t_1, t_2\}$, we can get $B'(t_2) > 0$. They are contradictory, that is, both t_1 and t_2 don't exist. Therefore, $M_I(t) \geq 0$ and $B(t) \geq 0$ for $t \geq 0$ when the initial value $M_I^0 \geq 0$ and $B^0 \geq 0$.

Finally, we prove that the solutions of model (1.1) are ultimately bounded. By using of the first two equation of model (1.1), we have

$$\frac{dM_U(t)}{dt} + \frac{M_I(t)}{dt} \leq \Lambda_U - \min\{\mu_U, \mu_I\}(M_U + M_I),$$

which implies that

$$\limsup_{t \to +\infty} (M_U(t) + M_I(t)) \leq \frac{\Lambda_U}{\min\{\mu_U, \mu_I\}} \triangleq \mathcal{M}.$$

And thus, the fourth equation of model (1.1) means that

$$\frac{dT(t)}{dt} \leq \Lambda_T + \sigma_M \mathcal{M} T - \mu_T T.$$

That is,

$$\limsup_{t \to +\infty} T(t) \leq \frac{\Lambda_T}{\mu_T - \sigma_M \mathcal{M}}.$$

From the fourth equation of (1.1) it follows that

$$T = \frac{\Lambda_T}{\mu_T - \sigma_M M_I} \leq \frac{\Lambda_T}{\mu_T - \sigma_M \mathcal{M}},$$

and that $T > 0$, so that $\Lambda_T / (\mu_T - \sigma_M \mathcal{M})$ is always positive. We assert that $B(t)$ is bounded. Otherwise, suppose that $B(t)$ is unbounded, which means $\lim_{t \to +\infty} B(t) = +\infty$. The non-negativity and boundedness of $M_U(t)$ implies there exists a sufficiently large time $t_3 > 0$, such that

$$\frac{dB}{dt} \leq r\mu_I \mathcal{M} - \gamma_U M_U B - \mu_B B < 0, \ t \geq t_3.$$

Then $\frac{dB}{dt} < 0$ means that $B(t)$ decreases as $t(t > t_3)$ increases until $\frac{dB}{dt} > 0$. It implies B can not grow unbounded, which contradicts with the assumption of unboundedness of B. We suppose that the maximum value of B is $\mathcal{B}$, therefore the total MTb bacteria load is bounded and denoted as $B(t) < \mathcal{B}$ for all $t \geq 0$. □

3. Equilibrium solutions

In this section, we mainly devote to the basic reproduction number and the existence of equilibria of model (1.1).

It is clear there always admits a bacterium-free equilibrium $P_0 = (M_{U0}, 0, 0, T_0)$, where $M_{U0} = \Lambda_U/\mu_U$, and $T_0 = \Lambda_T/\mu_T$. And then, following the approach of next-generation matrix[19], we can find the basic reproduction number $\mathcal{R}_0$ of model (1.1) to be

$$\mathcal{R}_0 = \frac{r\mu_I\beta\Lambda_U/\mu_U}{(\alpha_T\Lambda_T/\mu_T + \mu_I)(\gamma_U\Lambda_U/\mu_U + \mu_B)}.$$

Finally, in order to find the bacteria-present equilibrium $P_* = (M_U^*, M_I^*, B^*, T^*)$, we consider the following equations:

$$\begin{cases} \Lambda_U - \mu_U M_U - \beta B M_U = 0, \\ \beta B M_U - \alpha_T M_I T - \mu_I M_I = 0, \\ r\mu_I M_I - \gamma_U M_U B - \mu_B B = 0, \\ \Lambda_T + \sigma_M M_I T - \mu_T T = 0. \end{cases} \tag{3.1}$$

The first equation of (3.1) implies that

$$M_U = \frac{\Lambda_U}{\mu_U + \beta B}.$$

The second equation of (3.1) and the expression of M_U implies that

$$M_I = \frac{\Lambda_U\beta B}{(\mu_I + \alpha_T T)(\beta B + \mu_U)}.$$

Taking the expressions of M_U and M_I into the forth equation of (3.1), we have

$$\mu_T\alpha_T(\beta B + \mu_U)T^2 + [(\mu_I\mu_T - \Lambda_T\alpha_T)(\beta B + \mu_U) - \sigma_M\Lambda_U\beta B]T - \Lambda_T\mu_I(\beta B + \mu_U) = 0. \tag{3.2}$$

Obviously, when $B > 0$, we have $\mu_T\alpha_T(\beta B + \mu_U) > 0$, and $\Lambda_T\mu_I(\beta B + \mu_U) > 0$. It implies that Eq.(3.2) only exists one positive root $T(B)$, which satisfies

$$T(B) = \frac{(\Lambda_T\alpha_T - \mu_I\mu_T)(\beta B + \mu_U) + \sigma_M\Lambda_U\beta B + \sqrt{\Delta}}{2\mu_T\alpha_T(\beta B + \mu_U)}$$

with

$$\Delta = [(\mu_I\mu_T - \Lambda_T\alpha_T)(\beta B + \mu_U) - \sigma_M\Lambda_U\beta B]^2 + 4\Lambda_T\mu_I\mu_T\alpha_T(\beta B + \mu_U)^2.$$

On the other hand, taking the expressions of M_U and M_I into the third equation of (3.1), we can get

$$T(B) = \frac{\mu_I}{\alpha_T}\Big(\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U + \mu_B(\beta B + \mu_U)} - 1\Big). \tag{3.3}$$

In order to ensure $T(B) > 0$ in (3.3), we need to require

$$\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U + \mu_B(\beta B + \mu_U)} > 1.$$

Namely, when $\Lambda_U\beta r/(\Lambda_U\gamma_U + \mu_B\mu_U) \leq 1$, we can get

$$\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U + \mu_B(\beta B + \mu_U)} \leq \frac{\Lambda_U\beta r}{\Lambda_U\gamma_U + \mu_B\mu_U} \leq 1,$$

which implies that $T(B) \le 0$ in (3.3) when $\Lambda_U\beta r/\Lambda_U\gamma_U+\mu_B\mu_U \le 1$. Obviously, $\Lambda_U\beta r/\Lambda_U\gamma_U+\mu_B\mu_U \le 1$ inevitably leads to $\mathcal{R}_0 < 1$, Therefore, system (1.1) does not have the bacteria-present equilibrium when $\mathcal{R}_0 < 1$ and $\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U+\mu_B\mu_U} \le 1$.

In the following, we discuss the existence of the bacteria-present equilibrium when $\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U+\mu_B\mu_U} > 1$. For this reason, we denote

$$g(B) = \frac{(\Lambda_T\alpha_T - \mu_I\mu_T)(\beta B+\mu_U) + \sigma_M\Lambda_U\beta B + \sqrt{\Delta}}{2\mu_T\alpha_T(\beta B+\mu_U)},$$
$$f(B) = \frac{\mu_I}{\alpha_T}\left(\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U+\mu_B(\beta B+\mu_U)} - 1\right).$$

There exists an bacteria-present equilibrium if and only if there is an intersection point between $g(B)$ and $f(B)$ in the interval $(0, (\Lambda_U\beta r - \Lambda_U\gamma_U - \mu_B\mu_U)/\beta\mu_B)$.

Direct calculation indicates that

$$g'(B) = \frac{\sigma_M\Lambda_U\beta\alpha_T\mu_T\mu_U\{\sqrt{\Delta} - [(\mu_I\mu_T - \Lambda_T\alpha_T)(\beta B+\mu_U) - \sigma_M\Lambda_U\beta B]\}}{2a^2\sqrt{\Delta}} > 0,$$
$$f'(B) = \frac{-r\mu_I\Lambda_U\beta^2\alpha_T\mu_B}{[\alpha_T(\Lambda_U\gamma_U+\mu_B(\beta B+\mu_U))]^2} < 0,$$
$$f''(B) = \frac{2r\mu_I\Lambda_U\beta^3\alpha_T^3\mu_B^2(\Lambda_U\gamma_U+\mu_B(\beta B+\mu_U)}{[\alpha_T(\Lambda_U\gamma_U+\mu_B(\beta B+\mu_U))]^4} > 0.$$

Then $f(B)$ is monotonically decreasing convex function, and $g(B)$ is a monotonically increasing function. In addition, since

$$f(0) = \frac{\mu_I}{\alpha_T}\left(\frac{\Lambda_U r\beta}{\Lambda_U\gamma_U+\mu_B\mu_U} - 1\right) > 0, \quad g(0) = \frac{\Lambda_T}{\mu_T} > 0,$$

and $f(\infty) = -\mu_I/\alpha_T < 0$, we know that $f(B)$ and $g(B)$ intersect if and only if $f(0) > g(0)$, that is,

$$\frac{\Lambda_U\beta r}{\Lambda_U\gamma_U+\mu_B\mu_U} > \frac{\Lambda_T\alpha_T+\mu_I\mu_T}{\mu_I\mu_T}.$$

It implies that model (1.1) exists the bacteria-present equilibrium when $\mathcal{R}_0 > 1$. Furthermore, we know that system (1.1) also does not have the bacteria-present equilibrium when $\Lambda_U\beta r/(\Lambda_U\gamma_U+\mu_B\mu_U) \le 1$ and $\mathcal{R}_0 < 1$.

Summarizing the above analysis, we have the following result:

Theorem 3.1. *Model (1.1) always has the bacterium-free equilibrium $P_0 = (\Lambda_U/\mu_U, 0, 0, \Lambda_T/\mu_T)$. In addition, if $\mathcal{R}_0 > 1$, model (1.1) also has a unique the bacteria-present equilibrium $P^*(M_U^*, M_I^*, B^*, T^*)$, where*

$$M_U^* = \frac{\Lambda_U}{\mu_U+\beta B^*}, \quad M_I^* = \frac{\Lambda_U\beta B^*}{(\mu_I+\alpha_T T^*)(\beta B^*+\mu_U)},$$
$$T^* = \frac{(\Lambda_T\alpha_T - \mu_I\mu_T)(\beta B^*+\mu_U) + \sigma_M\Lambda_U\beta B^* + \sqrt{\Delta}}{2\mu_T\alpha_T(\beta B^*+\mu_U)},$$

and B^* satisfies $f(B^*) = g(B^*)$.

4. Global analysis

In this section, we mainly investigate the stability of the bacterium-free equilibrium P_0 and the bacteria-present equilibrium P^*.

Theorem 4.1. *If $R_0 < 1$, the bacterium-free equilibrium P_0 is globally asymptotically stable, while if $R_0 > 1$, the bacterium-free equilibrium P_0 is unstable.*

Proof. The Jacobian matrix of model (1.1) at P_0

$$J(P_0) = \begin{pmatrix} -\mu_U & 0 & -\beta\frac{\Lambda_U}{\mu_U} & 0 \\ 0 & -\alpha_T\frac{\Lambda_T}{\mu_T} - \mu_I & \beta\frac{\Lambda_U}{\mu_U} & 0 \\ 0 & r\mu_I & -\gamma_U\frac{\Lambda_U}{\mu_U} - \mu_B & 0 \\ 0 & \sigma_M\frac{\Lambda_T}{\mu_T} & 0 & -\mu_T \end{pmatrix}. \tag{4.1}$$

Therefore, the characteristic equation of the system (1.1) at P_0 is

$$f_0(\lambda) = (\lambda + \mu_U)(\lambda + \mu_T)f(\lambda) = 0, \tag{4.2}$$

where

$$f(\lambda) = \lambda^2 + \left(\gamma_U\frac{\Lambda_U}{\mu_U} + \mu_B + \alpha_T\frac{\Lambda_T}{\mu_T} + \mu_I\right)\lambda - \left(\alpha_T\frac{\Lambda_T}{\mu_T} + \mu_I\right)\left(\gamma_U\frac{\Lambda_U}{\mu_U} + \mu_B\right)(R_0 - 1).$$

It is clear that both $\lambda_1 = -\mu_U$ and $\lambda_2 = -\mu_T$ are the characteristic roots, and the remaining characteristic roots satisfy $f(\lambda) = 0$.

Because $\gamma_U\Lambda_U/\mu_U + \mu_B + \alpha_T\Lambda_T/\mu_T + \mu_I > 0$, and $(\alpha_T\Lambda_T/\mu_T + \mu_I)(\gamma_U\Lambda_U/\mu_U + \mu_B) > 0$, we know $f(\lambda) = 0$ has one positive real root if $R_0 > 1$, which implies that P_0 is unstable. While if $R_0 < 1$, the Routh-Hurwitz criterion implies that the roots of $f(\lambda) = 0$ both have negative real part, that is, P_0 is locally asymptotically stable.

Next, we give the global stability of P_0 by constructing the Lyapunov function. Let

$$V_0 = v_0M_U + mM_I + nB + kv_0T,$$

where

$$v_0(x) = x - 1 - \ln x,\ m = \frac{\Lambda_U\gamma_U}{\mu_U\mu_B} + 1,\ n = \frac{\beta\Lambda_U}{\mu_U\mu_B} \text{ and } k = \frac{\alpha_T}{\sigma_M}\left(\frac{\Lambda_U\gamma_U}{\mu_U\mu_B} + 1\right).$$

Then, we have

$$\begin{aligned}
\frac{dV_0}{dt} &= (1 - \frac{M_{U0}}{M_U})(\Lambda_U - \mu_UM_U - \beta BM_U) + m(\beta BM_U - \alpha_TM_IT - \mu_IM_I) \\
&\quad + n(r\mu_IM_I - \gamma_UM_UB - \mu_BB) + k(1 - \frac{T_0}{T})(\Lambda_T + \sigma_MM_IT - \mu_TT) \\
&= \frac{-\mu_U}{M_U}(M_U - M_{U0})^2 + (m\beta - \beta - n\gamma_U)BM_U + M_I(-m\mu_I + nr\mu_I - k\sigma_MT_0) \\
&\quad + B(-n\mu_B + \beta M_{U0}) - k\frac{\mu_T}{T}(T - T_0)^2 + M_IT(k\sigma_M - m\alpha_T) \\
&= \frac{-\mu_U}{M_U}(M_U - M_{U0})^2 + M_I\frac{r\beta\Lambda_U\mu_I\mu_T - (\alpha_T\Lambda_T + \mu_I\mu_T)(\gamma_U\Lambda_U + \mu_U\mu_B)}{\mu_B\mu_U\mu_T} - k\frac{\mu_T}{T}(T - T_0)^2 \\
&= \frac{-\mu_U}{M_U}(M_U - M_{U0})^2 + M_I\frac{(\alpha_T\Lambda_T + \mu_I\mu_T)(\gamma_U\Lambda_U + \mu_U\mu_B)(\mathcal{R}_0 - 1)}{\mu_B\mu_U\mu_T} - k\frac{\mu_T}{T}(T - T_0)^2 \\
&\le 0.
\end{aligned} \tag{4.3}$$

It is clear that the maximum invariant set contained in the set $\frac{dV_0}{dt} = 0$ is $\{P_0\}$. Therefore, applying the LaSalle-Lyapunov Theorem, we have that P_0 is globally asymptotically stable. □

Theorem 4.2. *If $\mathcal{R}_0 > 1$, then the bacteria-present equilibrium P^* is locally asymptotically stable.*

Proof. The Jacobian matrix of model (1.1) at the bacteria-present equilibrium P^* is:

$$J(P^*) = \begin{pmatrix} -\mu_U - \beta B^* & 0 & -\beta M_U^* & 0 \\ \beta B^* & -\alpha_T T^* - \mu_I & \beta M_U^* & -\alpha_T M_I^* \\ -\gamma_U B^* & r\mu_I & -\gamma_U M_U^* - \mu_B & 0 \\ 0 & \sigma_M T^* & 0 & \sigma_M M_I^* - \mu_T \end{pmatrix}. \tag{4.4}$$

Therefore, the characteristic equation of matrix $J(P^*)$ is

$$f^*(\lambda) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0, \tag{4.5}$$

where

$$\begin{aligned} b_1 =& \alpha_T T^* + \mu_I + \mu_U + \beta B^* + \gamma_U M_U^* + \mu_B + \frac{\Lambda_T}{T^*}, \\ b_2 =& (\mu_U + \beta B^*)(\alpha_T T^* + \mu_I) + (\alpha_T T^* + \mu_I + \mu_U + \beta B^* + \gamma_U M_U^* + \mu_B)\frac{\Lambda_T}{T^*} + \beta B^* \mu_B \\ &+ \mu_U(\gamma_U M_U^* + \mu_B^*) + \alpha_T M_I^* \sigma_M T^*, \\ b_3 =& \beta B^* \mu_B(\alpha_T T^* + \mu_I) + [(\mu_U + \beta B^*)(\alpha_T T^* + \mu_I) + \mu_U(\gamma_U M_U^* + \mu_B) + \beta B^* \mu_B]\frac{\Lambda_T}{T^*} \\ &+ \alpha_T M_I^* \sigma_M T^*(\mu_U + \beta B^* + \gamma_U M_U^* + \mu_B), \\ b_4 =& \alpha_T M_I^* \sigma_M T^* [\mu_U(\gamma_U M_U^* + \mu_B) + \beta B^* \mu_B] + \beta B^* \mu_B(\alpha_T T^* + \mu_I)\frac{\Lambda_T}{T^*}. \end{aligned}$$

It is clear that $b_i > 0$, $i = 1, 2, 3, 4$. In addition,

$$\Delta_2 = b_1 b_2 - b_3 > 0, \ \Delta_3 = (b_1 b_2 - b_3) b_3 - b_1^2 b_4 > 0.$$

The detailed proof process for $\Delta_2 > 0$ and $\Delta_3 > 0$ can be found in the appendix. Therefore, The Routh-Hurwitz criterion implies that the real parts of all roots of the characteristic equation $f^*(\lambda) = 0$ are less than 0. That is, the bacteria-present equilibrium P^* is locally asymptotically stable when $\mathcal{R}_0 > 1$. □

Theorem 4.3. *If $\mathcal{R}_0 > 1$ and $\mu_U \mu_B^2 / r\mu_I \beta \gamma_U \mathcal{M}^2 \geq 1$, then the bacteria-present equilibrium P^* is globally stable.*

Proof. We will prove the global stability of P^* by constructing a Lyapunov function. Let

$$\begin{aligned} V_* =& (a_1 + a_2)\left[M_U - M_U^* - M_U^* \ln\left(\frac{M_U}{M_U^*}\right)\right] + (a_3 + a_4)\left[M_I - M_I^* - M_I^* \ln\left(\frac{M_I}{M_I^*}\right)\right] \\ &+ \mathrm{a_5}\left[\mathrm{B} - \mathrm{B}^* - \mathrm{B}^* \ln\left(\frac{\mathrm{B}}{\mathrm{B}^*}\right)\right] + (\mathrm{a_6} + \mathrm{a_7})\left[\mathrm{T} - \mathrm{T}^* - \mathrm{T}^* \ln\left(\frac{\mathrm{T}}{\mathrm{T}^*}\right)\right], \end{aligned} \tag{4.6}$$

where a_1 is any positive constant, and

$$\begin{aligned} a_2 &= \left(\frac{\mu_U}{\beta B^* M_U^*}\frac{\mu_B}{\gamma_U} - 1\right)a_1, \ a_3 = \frac{\mu_U}{\beta B^* M_U^*}\frac{\mu_B}{\gamma_U}a_1, \ a_4 = \frac{\mu_U M_U^*}{\beta B^* M_U^*}a_1, \\ a_5 &= \frac{\mu_U M_U^*}{\gamma_U M_U^* B^*}a_1, \ a_6 = \frac{\mu_U \alpha_T M_I^*(M_U^* \gamma_U + \mu_B)}{\gamma_U \beta B^* M_U^* \mu_T}a_1, \\ a_7 &= \frac{\Lambda_T \mu_U \alpha_T (M_U^* \gamma_U + \mu_B)}{\sigma_M T^* \gamma_U \beta B^* M_U^* \mu_T}a_1. \end{aligned} \tag{4.7}$$

It is clear that $V_*(x) > 0$, and $V_*(P^*) = 0$ for $x \in \Gamma$. Then, directly taking the derivative of V_* yields that

$$\begin{aligned}\frac{dV_*}{dt} &= (a_1+a_2)(1-\frac{M_U^*}{M_U})(\Lambda_U - \mu_U M_U - \beta B M_U)\\ &+ (a_3+a_4)(1-\frac{M_I^*}{M_I})(\beta B M_U - \alpha_T M_I T - \mu_I M_I)\\ &+ a_5(1-\frac{B^*}{B})(r\mu_I M_I - \gamma_U M_U B - \mu_B B)\\ &+ (a_6+a_7)(1-\frac{T^*}{T})(\Lambda_T + \sigma_M M_I T - \mu_T T).\end{aligned} \tag{4.8}$$

In addition, by using of Eq.(3.1), we have

$$\begin{aligned}&\Lambda_U = \mu_U M_U^* + \beta B^* M_U^*,\ \mu_I = \frac{\beta \mathrm{B^* M_U^*}}{\mathrm{M_I^*}} - \frac{\alpha_\mathrm{T} \mathrm{M_I^* T^*}}{\mathrm{M_I^*}},\\ &\mu_B = \frac{r\mu_I M_I^*}{B^*} - \frac{\gamma_U M_U^* B^*}{B^*},\ \Lambda_T = -\sigma_M M_I^* T^* + \mu_T T^*.\end{aligned} \tag{4.9}$$

Taking (4.9) into (4.8), we can get

$$\begin{aligned}\frac{dV_*}{dt} &= (a_1+a_2)\left[\mu_\mathrm{U}\mathrm{M_U^*}\left(2-\frac{\mathrm{M_U^*}}{\mathrm{M_U}}-\frac{\mathrm{M_U}}{\mathrm{M_U^*}}\right)+\beta \mathrm{B^* M_U^*}\left(1-\frac{\mathrm{B M_U}}{\mathrm{B^* M_U^*}}+\frac{\mathrm{B}}{\mathrm{B^*}}-\frac{\mathrm{M_U^*}}{\mathrm{M_U}}\right)\right]\\ &+ (a_3+a_4)\left[\beta B^* M_U^*\left(\frac{BM_U}{B^*M_U^*}-\frac{M_I}{M_I^*}-\frac{BM_UM_I^*}{B^*M_U^*M_I}+1\right)+\alpha_T M_I^* T^*\left(\frac{T}{T^*}+\frac{M_I}{M_I^*}-\frac{M_IT}{M_I^*T^*}-1\right)\right]\\ &+ a_5\left[r\mu_I M_I^*\left(\frac{M_I}{M_I^*}-\frac{B}{B^*}-\frac{M_IB^*}{M_I^*B}+1\right)+\gamma_U M_U^* B^*\left(-\frac{M_UB}{M_U^*B^*}+\frac{B}{B^*}+\frac{M_U}{M_U^*}-1\right)\right]\\ &+ (a_6+a_7)\left[\sigma_M M_I^* T^*\left(-1+\frac{M_IT}{M_I^*T^*}-\frac{M_I}{M_I^*}+\frac{T^*}{T}\right)+\mu_T T^*(2-\frac{T}{T^*}-\frac{T^*}{T})\right],\end{aligned}$$

Denoting $y_1 = \frac{M_U}{M_U^*}$, $y_2 = \frac{M_I}{M_I^*}$, $y_3 = \frac{B}{B^*}$, and $y_4 = \frac{T}{T^*}$, we have

$$\begin{aligned}\frac{dV_*}{dt} &= (a_1+a_2)\left[\mu_U M_U^*\left(2-\frac{1}{y_1}-y_1\right)+\beta B^* M_U^*\left(1+y_3-\frac{1}{y_1}-y_3y_1\right)\right]\\ &+ (a_3+a_4)\left[\beta B^* M_U^*\left(y_3y_1-y_2-\frac{y_3y_1}{y_2}+1\right)+\alpha_T M_I^* T^*\left(y_4+y_2-y_2y_4-1\right)\right]\\ &+ a_5\left[r\mu_I M_I^*\left(y_2-y_3-\frac{y_2}{y_3}+1\right)+\gamma_U M_U^* B^*\left(-y_1y_3+y_3+y_1-1\right)\right]\\ &+ (a_6+a_7)\left[\sigma_M M_I^* T^*\left(-1+y_2y_4+\frac{1}{y_4}-y_2\right)+\mu_T T^*(2-y_4-\frac{1}{y_4})\right].\end{aligned} \tag{4.10}$$

Furthermore, by using of

$$\begin{aligned}(a_1+a_2)\beta B^* M_U^* = a_3\beta B^* M_U^* = a_5\mu_B B^*,\\ a_1\mu_U M_U^* = a_4\beta B^* M_U^* = a_5\gamma_U M_U^* B^*,\\ (a_6+a_7)\sigma_M M_I^* T^* = a_6\mu_T T^* = (a_3+a_4)\,\alpha_T M_I^* T^*,\end{aligned}$$

Eq.(4.10) can be rewritten as

$$\frac{dV_*}{dt} = a_2\mu_U M_U^*\left(2-\frac{1}{y_1}-y_1\right)+(a_3+a_4)\,\beta B^* M_U^*\left(3-\frac{1}{y_1}-\frac{y_2}{y_3}-\frac{y_1y_3}{y_2}\right)+a_7\mu_T T^*\left(2-y_4-\frac{1}{y_4}\right).$$

Obviously, $a_i > 0$, $i = 3, 4, 7$, in (4.7) when $a_1 > 0$. In addition, $\mu_U\mu_B^2/r\mu_I\beta\gamma_U\mathcal{M}^2 \geq 1$ and $a_1 > 0$ can ensure $a_2 \geq 0$. Therefore, we can get $V_*'(x) \leq 0$ for any $x \in \Gamma$, and $V_*'(x) = 0$ if and only if $x = P^*$. That is, the LaSalle-Lyapunov Theorem implies that P^* is globally asymptotically stable.

In order to verify that the bacteria-present equilibrium P^* is not globally stable when $\mathcal{R}_0 > 1$ and $\mu_U\mu_B^2/r\mu_I\beta\gamma_U\mathcal{M}^2 < 1$, numerical simulations are carried out below. The parameters in the simulations are $\Lambda_U = 1000$, $\beta = 2 \times 10^{-9}$, $\mu_U = 0.0028$, $\alpha_T = 3 \times 10^{-5}$, $\mu_I = 0.001$, $r = 100$, $\gamma_U = 1.2 \times 10^{-7}$, $\mu_B = 0.012$, $\Lambda_T = 0.001$, $\sigma_M = 0.008$, and $\mu_T = 0.33$, then $\mathcal{R}_0 = 1.3020$ and $\mu_U\mu_B^2/r\mu_I\beta\gamma_U\mathcal{M}^2 = 0.0168$. Taking two different sets of initial values, the simulation results of B over time are shown in the following Fig.1, which shows that the bacteria-present equilibrium P^* is not globally stable at this time.

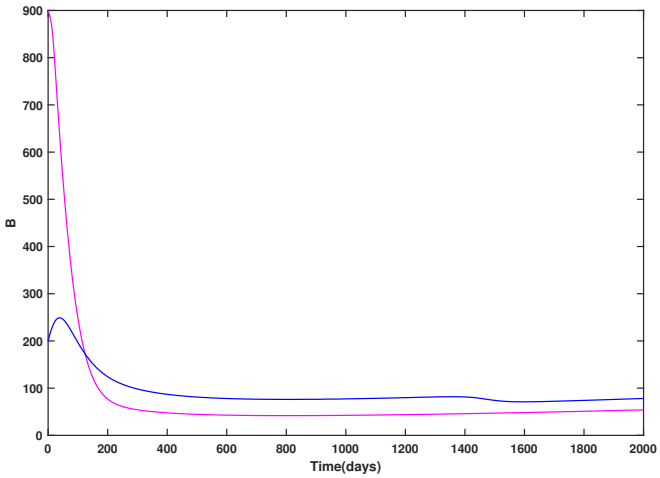


FIGURE 1. The not globally stable is formed after Mtb invades the host when $\mathcal{R}_0 > 1$ and $\frac{\mu_U\mu_B^2}{r\mu_I\beta\gamma_U\mathcal{M}^2} < 1$.

□

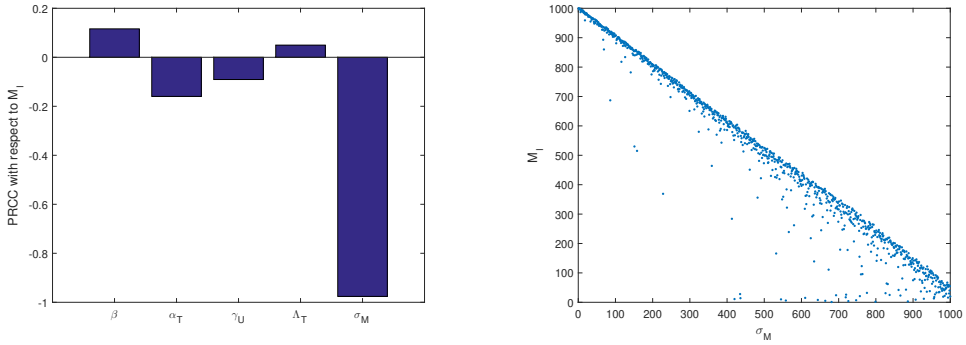
5. **The sensitivity analysis and numerical simulations**

The quantity and toxicity of Mtb in the host play an important role in whether LTBIs will develop into the active TB. We will chose five parameters related to M_I and B, that is, β, α_T, γ_U, Λ_T and σ_M, to show the impact of these parameters on Mtb in the host. To this end, we use the sensitivity analysis based on Latin Hypercube Sampling (LHS) to illustrate it. The parameter ranges of model (1.1) are put in Table 1.

Both Fig.2 and Fig.3 display that the activation rate σ_M of immune T cells by infected macrophages M_I has the greatest impact on Mtb in the host. It means that if infected macrophages can stimulate the immune system to produce more immune T-cells, this will inhibit the survival, growth and reproduction of Mtb in the host. That is, the immune system of LTBIs determines whether they are persistent LTBIs or active TB.

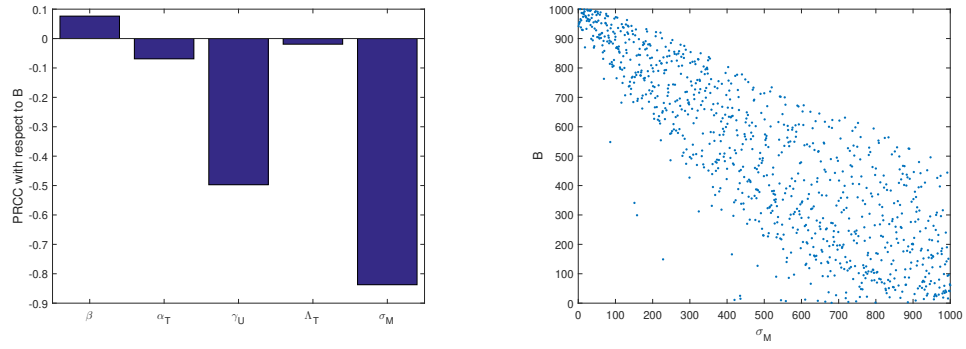
TABLE 1. Parameter values

Parameter	Value	Unit	Reference
Λ_U	$(600, 1000)$	day^{-1}	[20]
μ_U	$(0.002, 0.0033)$	day^{-1}	[20]
β	$(1 \times 10^{-6}, 3 \times 10^{-6})$	day^{-1}	[20]
α_T	$(1 \times 10^{-5}, 5 \times 10^{-5})$	day^{-1}	[20]
μ_I	0.011	day^{-1}	[20]
r	$(0.02, 0.8)$	day^{-1}	[20]
γ_U	$(5 \times 10^{-6}, 1.9 \times 10^{-6})$	day^{-1}	Estimate
μ_B	0.012	day^{-1}	[17]
Λ_T	6.6	day^{-1}	[22]
σ_M	$(1 \times 10^{-3}, 0.01)$	day^{-1}	[20]
μ_T	0.33	day^{-1}	[20]



(a) The sensitivity analysis (b) The scatter plots

FIGURE 2. The sensitivity analysis of M_I on part parameter.



(a) The sensitivity analysis (b) The scatter plots

FIGURE 3. The sensitivity analysis of B on part parameter.

In the following we verify numerically the existence and stability of equilibria under conditions according to the results given in last sections. Taking the parameters $\Lambda_U = 1000$, $\beta = 2 \times 10^{-6}$, $\mu_U = 0.0028$, $\alpha_T = 3 \times 10^{-5}$, $\mu_I = 0.011$, $r = 0.2$, $\gamma_U = 5 \times 10^{-6}$, $\mu_B = 0.012$, $\Lambda_T = 6.6$, $\sigma_M = 0.008$,

and $\mu_T = 0.33$, we can get $\mathcal{R}_0 = 0.0754 < 1$. Correspondingly, Fig.4 displays that Mtb invading the host is eliminated, and due to the strong response of activated infected macrophages, the initial population of Mtb and infected macrophages is reduced to zero. It was also observed that bacteria were cleared before a large number of specific immunity could be excited. The human body in this state is not infected, and the human body is healthy.

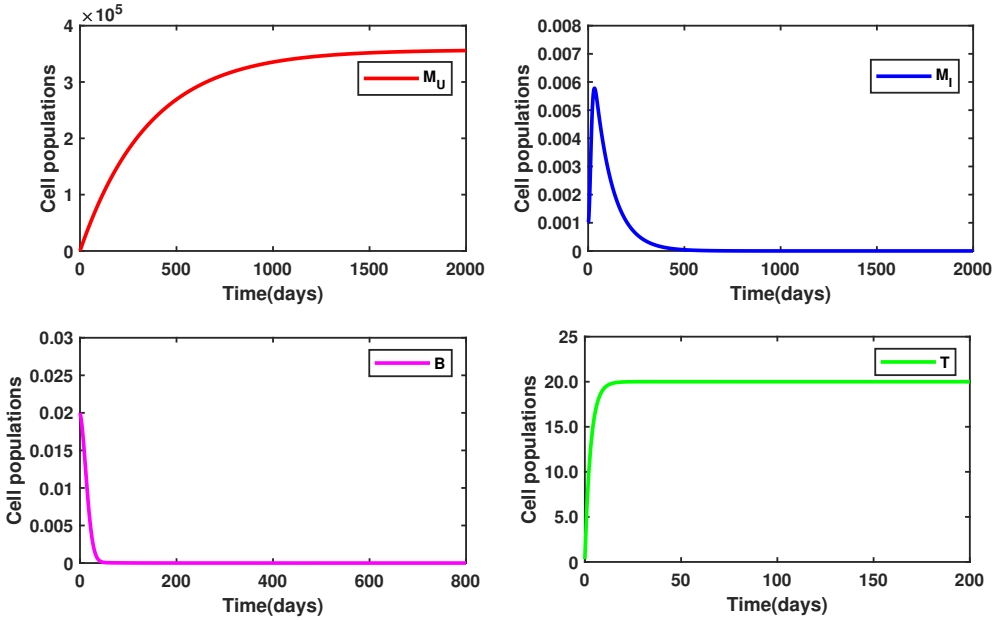


FIGURE 4. The eliminated stage is formed after Mtb invades the host when $\mathcal{R}_0 < 1$.

Taking the parameters $\beta = 3 \times 10^{-6}$, $r = 0.8$, $\gamma_U = 1.9 \times 10^{-6}$, and keeping the other parameters consistent with Fig.4, we have $\mathcal{R}_0 = 1.1770 > 1$. It implies that Mtb invading the host will survive, even grow and reproduce in macrophages. Fig.5 shows that the number of activated infected macrophages is much greater than the number of infected macrophages, and Mtb is controlled by immune cells, which is the incubation period of TB, that is, LTBIs. At this time, although Mtb is present in the body, the latently infected individual is not contagious and has no obvious symptoms. If the immune system is weakened at this time, it may lead to reactivation of the disease, which can develop into active TB.

At last, since active TB is not available for the parameter values in Table 1, we choose $\beta = 2 \times 10^{-3}$, $r = 35$, $\gamma_U = 1.2 \times 10^{-7}$, and keeping the other parameters consistent with the Fig.4, we have $\mathcal{R}_0 = 432160 > 1$. It is clear that Mtb invading the host will survive , even grow and reproduce in macrophages. Fig.6 shows that Mtb, T cells, activated infected macrophages and infected macrophages grow rapidly during the early stages of infection, after which the infected macrophages are drastically reduced by the outbreak, leading to the release of a large number of bacteria, causing a large increase in the bacterial population uncontrolled by the immune cells. It is clear that the infection is out of control and is active TB. At this time, the individual is contagious and shows obvious symptoms.

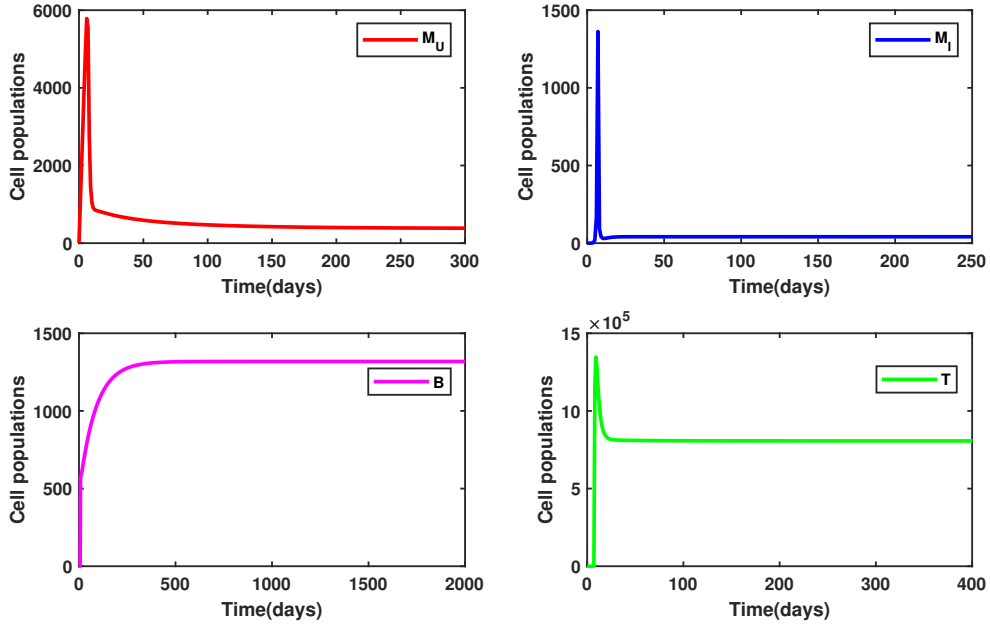


FIGURE 6. The active stage is formed after Mtb invades the host when $\mathcal{R}_0 > 1$.

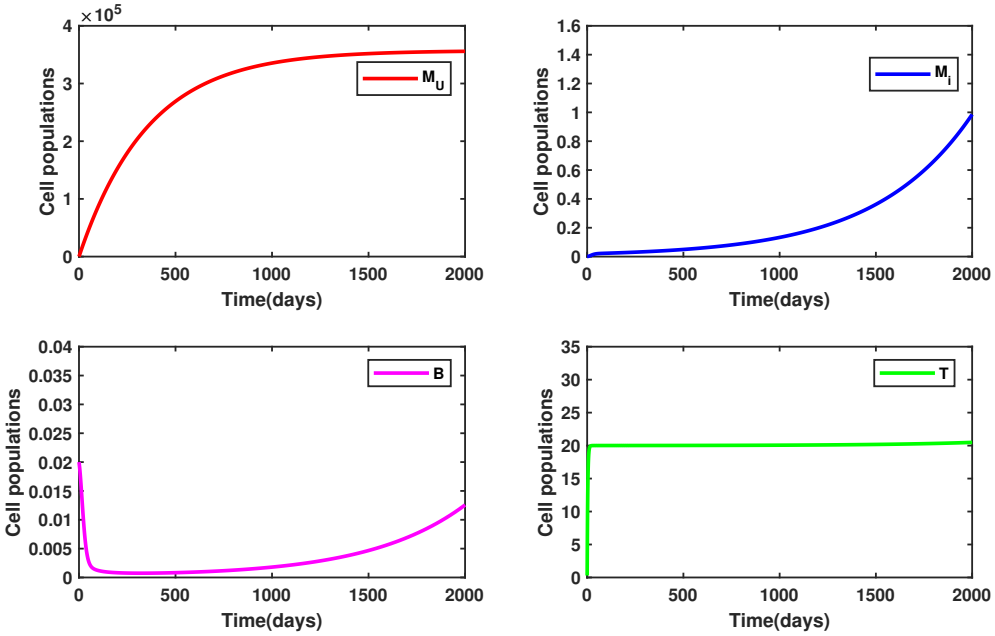


FIGURE 5. The latent stage is formed after Mtb invades the host when $\mathcal{R}_0 > 1$.

6. Conclusion

Based on the process of action of Mtb and the immune system, we establish a mathematical model describing the formation of TB granulomas. For this model, we demonstrate the existence and the global stability of the bacteria-free equilibrium and the bacteria-present equilibrium by constructing appropriate Lyapunov functions, followed by sensitivity analysis and numerical simulation. The main purpose of the study is to analyze the change trend of Mtb and immune cells in three different stages (clearance, latent infection and active TB) after Mtb invaded the host.

The results showed that when $R_0 < 1$, the infection rate β was smaller, so the number of infected macrophages was less. And the average number of bacteria released by infected macrophages r is smaller, so the number of bacteria released is less. When the number of bacteria is low, a large increase in activated infected macrophages kill the bacteria directly. At this time, the individual is not infected and is healthy; When $R_0 > 1$, the infection rate β and the average number of bacteria released by infected macrophages r become larger, while the phagocytosis rate of bacteria by activated infected macrophages γ_U becomes smaller, so the number of infected macrophages becomes larger, and the number of bacteria released also increases. As the number of bacteria increases, but the number is not large, the bacteria will be controlled by immune cells, and the number of activated infected macrophages at this time is much greater than the number of Mtb. This condition in which the individual has been infected, but there are no contagious and obvious symptoms, it is the incubation period of TB, that is, latent infection. A weakened immune system due to malnutrition, age, etc., will cause a large number of bacteria to grow uncontrolled by immune cells, resulting in uncontrollable infection and eventually developing active TB. At this time, the individual has TB, which is contagious and accompanied by obvious symptoms, such as, fever, cough, night sweats, etc., and needs timely treatment.

References [4] and [20] proposed that cytotoxic T lymphocytes (CTL) and tumor necrosis factor (TNF) induce apoptosis of infected macrophages, which releases some of the bacteria. Therefore, a mathematical model of TB granuloma that includes these cells should be considered for our future studies.

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Appendix

In this section, we will provide the detailed proof of $\Delta_2 > 0$, and $\Delta_3 > 0$.

Let

$$A = \alpha_T T^* + \mu_I, \quad C = \gamma_U M_U^* + \mu_B, \quad D = \alpha_T M_I^* \sigma_M T^*, \quad H = \mu_U + \beta B^*, \quad E = \frac{\Lambda_T}{T^*}.$$

Then, we have

$$\begin{aligned}\Delta_2 =& A\left[HA + \mu_U C + D + (A + H + C)\frac{\Lambda_T}{T^*}\right] + (H + \gamma_U M_U^*)\left[HA + \mu_U C + \beta B^* \mu_B\right.\\ &\left.+(A + H + C)\frac{\Lambda_T}{T^*}\right] + \frac{\Lambda_T}{T^*}\left[\beta B^* \mu_B + (A + H + C)\frac{\Lambda_T}{T^*} + D\right]\\ &+ \mu_B\left[HA + \mu_U C + \beta B^* \mu_B + (A + \mu_U + C)\frac{\Lambda_T}{T^*}\right] > 0,\end{aligned}$$

and

$$\begin{aligned}\Delta_3 =& \mu_U A^2\big[\beta B^* \mu_B A + (HA + \mu_U C + \beta B^* \mu_B)E + DH\big] + \beta B^* A^2\big[\beta B^* \mu_B A + (HA + \mu_U C + \beta B^* \mu_B)E\\ &+D(H + \gamma_U M_U^*)\big] + \mu_U AC\big[\beta B^* \mu_B A + (HA + \mu_U C + \beta B^* \mu_B)E\big] + A(A + \mu_U)E\big[(HA + \mu_U C\\ &+\beta B^* \mu_B)E + D(H + C)\big] + \beta B^* AE\big[(HA + \mu_U C + \beta B^* \mu_B)E + D(H + \gamma_U M_U^*)\big] + ACE\big[(AH\\ &+\mu_U C + \beta B^* \mu_B)E + D(\beta B^* + C)\big] + AD\big[\beta B^* \mu_B A + HAE + D(H + C)\big] + \mu_U(H + \gamma_U M_U^*)A\\ &+\big[\beta B^* \mu_B A(HA + \mu_U C + \beta B^* \mu_B)E + DH\big] + \beta B^*(H + \gamma_U M_U^*)A\big[\beta B^* \mu_B A + (HA + \mu_U C\\ &+\beta B^* \mu_B)E + D(H + \gamma_U M_U^*)\big] + (H + \gamma_U M_U^*)(\mu_U C + \beta B^* \mu_B)\big[\{\beta B^* \mu_B A + (AH + \mu_U C + \beta B^*\\ &\mu_B)E\big] + (H + \gamma_U M_U^*)AE\big[(AH + \mu_U C + \beta B^* \mu_B)E + D(H + C)\big] + \mu_U \gamma_U M_U^* E^2(HA + \mu_U C\\ &+\beta B^* \mu_B) + \gamma_U M_U^*(\beta B^* + \gamma_U M_U^*)E\big[(AH + \mu_U C + \beta B^* \mu_B)E + D(H + C)\big] + \mu_U(H + \gamma_U M_U^*)\\ &E\big[(HA + \mu_U C + \beta B^* \mu_B)E + DH\big] + \beta B^*(H + \gamma_U M_U^*)E\big[(HA + \mu_U C + \beta B^* \mu_B)E + D(H\\ &+\gamma_U M_U^*)\big] + \mu_B HE\big[(\mu_U A + \mu_U C + \beta B^* \mu_B)E\big] + \mu_B \gamma_U M_U^* E\big[(\mu_U A + \mu_U C + \beta B^* \mu_B)E\\ &+D(H + C)\big] + \beta B^* \mu_B E\big[\beta B^* \mu_B A + (AH + \mu_U C + \beta B^* \mu_B)E + D(H + C)\big] + (A + H\\ &+\gamma_U M_U^*)E^2\big[(AH + \mu_U C + \beta B^* \mu_B)E + D(H + C)\big] + DE\big[\beta B^* \mu_B A + AHE + D(H + C)\big]\\ &+\mu_B E^2\big[(\mu_U A + \mu_U C + \beta B^* \mu_B)E + D(H + C)\big] + \mu_B \beta B^* A\big[\beta B^* \mu_B A + (HA + \mu_U C + \beta B^* \mu_B)E\big]\\ &+\mu_B \mu_U A\big[\beta B^* \mu_B A + (HA + \mu_U C + \beta B^* \mu_B)E + D\mu_U\big] + \mu_B^2 \beta B^*\big[\beta B^* \mu_B A + (\mu_U A + \mu_U C\\ &+\beta B^* \mu_B)E\big] + \mu_B \mu_U C\big[\beta B^* \mu_B A + (HA + \mu_U C + \beta B^* \mu_B)E\big] + \mu_B^2 E\big[(\mu_U A + \mu_U C + \beta B^* \mu_B)E\\ &+D(\mu_U + C)\big] + \mu_B \mu_U E\big[(HA + \mu_U C + \beta B^* \mu_B)E + DH\big] + \mu_B \gamma_U M_U^* E\big[(HA + \mu_U C + \beta B^* \mu_B)E\\ &+D(H + C)\big] + \mu_B AE\big[\beta B^* \mu_B A + (\mu_U A + \mu_U C + \beta B^* \mu_B)E + D(H + C)\big] + AD\beta B^* \mu_B \mu_U\\ &> 0.\end{aligned}$$

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