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A Mathematical Model of in-Host Tuberculous Granuloma*

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Abstract Tuberculosis is the second biggest infectious disease killer after coronavirus. In this paper, we analyze a mathematical model of in-host tuberculous granuloma, obtaining the basic reproduction number, as well as the existence and stability of equilibrium points. The sensitivity analysis provides parameters that have a significant effect on model dynamics. Finally, changes in the number of immune cells, infected macrophages and Mycobacterium tuberculosis are analyzed by numerical simulation of three disease states: clearance, latent infection and active tuberculosis. The results suggest that the immune mechanism determing whether an infected individual will suffer from active or latent tuberculosis is the ability of activated infected macrophages to kill Mycobacterium tuberculosis.

Keywords Tuberculous granuloma, immune cell, the sensitivity analysis, stability

MSC(2010) 37N25, 92D30.

1. Introduction

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1]. Therefore, the study of the dynamics of the immune response within the granuloma is crucial for the prevention and treatment of TB.

About a quarter of the global population is estimated to have been infected with TB, but most people will not go on to develop TB. They either clear the infection, or experience latent infection [1]. These latent infection are neither sick nor contagious, but they are at greater risk of developing TB, especially those with weakened immune systems. Without treatment, the death rate from TB disease is high (about 50%) [1]. Providing them with TB prevention and treatment measures not only protects them from the disease, but also reduces the risk of transmission in the community. Understanding the dynamics of the immune response is critical to elucidating the differences between infected individuals and those with active disease.

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Nowadays, mathematical models are widely used to study the factors that influence the progression of TB infection [2–8]. We assume that:

1) As soon as Mycobacterium tuberculosis(Mtb) invades, macrophages are activated, that is, only activated and infected macrophages are considered;

2) Mtb is phagocytosed by macrophages and is either cleared or infects the macrophages. When the number of Mtb inside the macrophage reaches its limit, it explodes and releases Mtb outside the macrophage. Mtb outside macrophages grows in a linear manner;

3) in the event of a non-specific immune response, T cells are activated in a logistic manner induced by infected macrophages;

4) the role of cytokines in the immune response is expressed only through immune T cells and is not considered separately.

Based on the above assumptions and [3, 9], we study a four-dimensional ODE in-host TB granuloma model (1.1) that includes linear growth of Mtb. Model (1.1) includes activated infected macrophages($\bar{M}_U$), infected macrophages ($\bar{M}_I$), extracellular Mtb($\bar{B}$) and immune T cells($\bar{T}$). Activation, infection and death of activated infected macrophages($\bar{M}_U$) are tagged with Λ_U, $\bar{\beta}$ and μ_U. Infected macrophages($\bar{M}_I$) are cleared by T cells at the rate $\bar{\alpha}_T$. The death rate of infected macrophages($\bar{M}_I$) is μ_I. Recruitment of extracellular Mtb($\bar{B}$) resulting cell division or release by apoptosis of infected macrophages. The bacteria division is modelled in a linear manner, at a constant growth rate(Λ_B). The average number of bacteria released by apoptosis of infected macrophages is $\bar{r}$. The death rate of immune T cells($\bar{T}$) is expressed as μ_T. Infected macrophages($\bar{M}_I$) can activate T cells($\bar{T}$), expressed as $(1-\frac{\bar{T}}{T_{max}})\bar{k}_I\bar{M}_I$, where $\bar{k}_I$ is the growth rate of T cells, and T_{max} is the maximum population level of T cells. Our mathematical model of in-host TB granuloma is written like this:

$$\begin{cases} \dfrac{\mathrm{d}\bar{M}_U}{\mathrm{d}t} = \Lambda_U - \mu_U\bar{M}_U - \bar{\beta}\bar{B}\bar{M}_U, \\ \dfrac{\mathrm{d}\bar{M}_I}{\mathrm{d}t} = \bar{\beta}\bar{B}\bar{M}_U - \bar{\alpha}_T\bar{M}_I\bar{T} - \mu_I\bar{M}_I, \\ \dfrac{\mathrm{d}\bar{B}}{\mathrm{d}t} = \Lambda_B\bar{B} + \bar{r}\mu_I\bar{M}_I - \bar{\gamma}_U\bar{M}_U\bar{B} - \mu_B\bar{B}, \\ \dfrac{\mathrm{d}\bar{T}}{\mathrm{d}t} = (1-\dfrac{\bar{T}}{T_{max}})\bar{k}_I\bar{M}_I - \mu_T\bar{T}, \end{cases} \tag{1.1}$$

In order to reduce the number of parameters, we introduce the following variables

$$M_U = \frac{\bar{M}_U}{\Lambda_U/\mu_U},\ M_I = \frac{\bar{M}_I}{\Lambda_U/\mu_U},\ B = \frac{\bar{B}}{\mu_U^2/\Lambda_B^2},\ T = \frac{\bar{T}}{T_{max}}.$$

The system(1.1) becomes

$$\begin{cases} \dfrac{\mathrm{d}M_U}{\mathrm{d}t} = \mu_U - \mu_U M_U - \beta B M_U, \\ \dfrac{\mathrm{d}M_I}{\mathrm{d}t} = \beta B M_U - \alpha_T M_I T - \mu_I M_I, \\ \dfrac{\mathrm{d}B}{\mathrm{d}t} = \Lambda_B B + r M_I - \gamma_U M_U B - \mu_B B, \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = (1-T)k_I M_I - \mu_T T, \end{cases} \tag{1.2}$$

where

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$$\alpha_T = \bar{\alpha}_T T_{max},\ \gamma_U = \frac{\bar{\gamma}_U \Lambda_U}{\mu_U},\ k_I = \frac{\bar{k}_I \Lambda_U}{T_{max}\mu_U},\ \beta = \frac{\bar{\beta}\mu_U^2}{\Lambda_B^2},\ r = \frac{\bar{r}\Lambda_B^2 \Lambda_U \mu_I}{\mu_U^3}.$$

The aim of this paper is to study the dynamical behaviour of a mathematical model of in-host TB granuloma. The paper is organised as follows. In section 2, the well-posedness of system (1.2) is given. In section 3, the existence of equilibrium points is given. In section 4, the global stability of the equilibrium points is proved. In section 5, sensitivity analyses of important parameters are carried out, followed by numerical simulations of different infection states in which Mtb enters the human body, with specific analyses. Finally, we give discussion and conclusions.

2. Well-posedness

In this section, we will study the non-negativity and ultimately boundedness of the solutions of model (1.2) with non-negativity initial conditions.

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* (1.2) *stays in the positively invariant cone $\mathbb{R}^4_+$ and is bounded in the region*

$$\Omega = \{(\mathrm{M_U}, \mathrm{M_I}, \mathrm{B}, \mathrm{T}) \in \mathrm{R}^4_+ : \mathrm{M_U} + \mathrm{M_I} \leq \frac{\mu_\mathrm{U}}{\mathrm{a}}, \mathrm{B} \leq \mathrm{B_M}, \mathrm{T} \leq \mathrm{T_M}\}, \tag{2.1}$$

where, $a = min\{\mu_U, \mu_I\}$, $T_M = \frac{k_I \mu_U}{k_I \mu_U + a\mu_T}$, $B_M = \frac{\mathrm{r}\mu_\mathrm{U}}{\mathrm{a}(\mu_\mathrm{B} - \Lambda_\mathrm{B})}$ and $\mu_B > \Lambda_\mathrm{B}$.

Proof. We first prove the non-negativity of the solutions $(M_U(t), M_I(t), B(t), T(t))$ of model (1.2) with the non-negative initial $(M_U(0), M_I(0), B(0), T(0))$.

The first equation of model (1.2) implies that

$$M_U(t) = e^{-\int_0^t (\mu_U + \beta B(s))\, ds}\Big(\int_0^t \mu_U e^{\int_s^t (\mu_U + \beta B(u))\, du}\, ds + M_U(0)\Big).$$

It is easy to see that $M_U(t) > 0$, $t > 0$ if $M_U(0) \geq 0$.

By the second and third equations of model (1.2), we can get

$$M_I(t) = e^{-\int_0^t (\alpha_T T(s) + \mu_I)\, ds}\Big(\int_0^t \beta B(s) M_U(s) e^{\int_s^t (\alpha_T T(u) + \mu_I)\, du}\, ds + M_I(0)\Big),$$

$$B(t) = e^{-\int_0^t (\gamma_U M_U(s) + \mu_B - \Lambda_B)\, ds}\Big(\int_0^t r M_I(s) e^{\int_s^t (\gamma_U M_U(u) + \mu_B - \Lambda_B)\, du}\, ds + B(0)\Big).$$

It implies that $M_I(t) \geq 0$, $t \geq 0$ when $B(t) \geq 0$, $t \geq 0$, and $B(t) \geq 0$, $t \geq 0$, when $M_I(t) \geq 0$, $t \geq 0$. We suppose that $M_I(t) < 0$ and $B(t) < 0$. Since the initial value $M_I(0) \geq 0$ and $B(0) \geq 0$, the continuous dependence of the solution on the initial value implies the existence of $t_1 > 0$, and $t_2 > 0$, such that

$$M_I(t_1) = 0, \begin{cases} M_I(t) > 0, t < t_1, \\ M_I(t) < 0, t > t_1, \end{cases} \quad B(t_2) = 0, \begin{cases} B(t) > 0, t < t_2, \\ B(t) < 0, t > t_2. \end{cases}$$

Without loss of generality, we assume that $t_1 \leq t_2$, then $B(t) > 0$ for $t < t_2$, and

$$\begin{aligned} M_I(t_1) =& e^{-\int_0^{t_1} (\alpha_T T(s) + \mu_I) ds} \\ & \left(\int_0^{t_1} \beta B(s) M_U(s) e^{\int_s^{t_1} (\alpha_T T(u) + \mu_I) du} ds + M_I(0)\right) > 0, \end{aligned}$$

which contradicts $M_I(t_1) = 0$. That is, t_1 does not exist. Therefore $M_I(t) \geq 0$, $t \geq 0$.

Similarly, if $t_1 \geq t_2$, we have $M_I(t) > 0$ for $t < t_1$, then

$$\begin{aligned} B(t_2) =& e^{-\int_0^{t_2}(\gamma_U M_U(s)+\mu_B-\Lambda_B)ds} \\ & \left(\int_0^{t_2} rM_I(s)e^{\int_s^{t_2}(\gamma_U M_U(u)+\mu_B-\Lambda_B)du}ds + B(0)\right) > 0, \end{aligned}$$

which contradicts $B(t_2) = 0$. That is, t_2 does not exist. Therefore $B(t) \geq 0$, $t > 0$.

Furthermore, from the fourth equation of (1.2), we have

$$T(t) = e^{-\int_0^t(k_I M_I(s)+\mu_T)ds}\left(\int_0^t k_I M_I(s)e^{\int_s^t(k_I M_I(u)+\mu_T)du}ds + T(0)\right).$$

It is clear that $T(t) \geq 0$, $t > 0$ when $T(0) \geq 0$ since $M_I(t) \geq 0$.

Summarizing the above analysis, we know the solution $(M_U(t), M_I(t), B(t), T(t))$ of model (1.2) with the non-negative initial value $\{M_U(0), M_I(0), B(0), T(0)\}$ is non-negative.

Next, we prove the boundedness of the solutions of model (1.2). The first equation of system (1.2) implies that

$$M_U' \leq \mu_U - \mu_U M_U,$$

which implies that $\limsup_{t\to\infty} M_U(t) \leq 1$.

Adding the first and second equations in model (1.2), and letting $a = \min\{\mu_U, \mu_I\}$, we obtain

$$(M_U + M_I)' \leq \mu_U - a(M_U + M_I).$$

That is, $\limsup_{t\to\infty}(M_U(t) + M_I(t)) \leq \frac{\mu_U}{a}$.

According to the third equation of system (1.2), and $M_I \leq \frac{\mu_U}{a} - M_U \leq \frac{\mu_U}{a}$, we have

$$B' \leq r\frac{\mu_U}{a} - (\mu_B - \Lambda_B)B.$$

It means that $\limsup_{t\to\infty} B \leq \frac{\mathrm{r}\mu_\mathrm{U}}{\mathrm{a}(\mu_\mathrm{B}-\Lambda_\mathrm{B})} \triangleq \mathrm{B_M}$. Obviously, $B > 0$ if and only if $\mu_B > \Lambda_B$.

By the fourth equation of the system (1.2), and $M_I \leq \frac{\mu_U}{a} - M_U \leq \frac{\mu_U}{a}$, we get

$$\begin{aligned} T' &= (1-T)k_I M_I - \mu_T T \\ &= k_I M_I - T k_I M_I - \mu_T T. \end{aligned}$$

Thus, we have $\limsup_{t\to\infty} T \leq \frac{k_I\mu_U}{k_I\mu_U + a\mu_T} \triangleq T_M$. Therefore, the solutions $(M_U(t), M_I(t), B(t), T(t))$ of the system (1.2) are bounded. □

3. Equilibrium solutions

In this section, we focus on the basic reproduction number and the existence of equilibria of the model (1.2).

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It is clear that there always exists the bacterium-free equilibrium $P_0 = (1, 0, 0, 0)$. And then, following the approach of next-generation matrix [11], we can find the basic reproduction number $\mathcal{R}_0$ of model (1.2) to be

$$\mathcal{R}_0 = \frac{r\beta}{\mu_I(\gamma_U + \mu_B - \Lambda_B)}.$$

Now, in order to find the bacteria-present equilibrium $P_1 = (M_U^*, M_I^*, B^*, T^*)$, we consider the following equations:

$$\begin{cases} \mu_U - \mu_U M_U^* - \beta B^* M_U^* = 0, \\ \beta B^* M_U^* - \alpha_T M_I^* T^* - \mu_I M_I^* = 0, \\ \Lambda_B B^* + r M_I^* - \gamma_U M_U^* B^* - \mu_B B^* = 0, \\ (1 - T^*) K_I M_I^* - \mu_T T^* = 0. \end{cases} \tag{3.1}$$

The fourth equation of (3.1) implies that

$$M_I^* = \frac{\mu_T T^*}{(1 - T^*)k_I}. \tag{3.2}$$

On the other hand, the first equation of (3.1) implies that

$$B^* = \frac{\mu_U - \mu_U M_U^*}{\beta M_U^*}. \tag{3.3}$$

From the second and third equations of (3.1), we get the following relationship

$$\frac{B^*}{M_I^*} = \frac{\alpha_T T^* + \mu_I}{\beta M_U^*}, \tag{3.4}$$

$$\frac{B^*}{M_I^*} = \frac{r}{\gamma_U M_U^* + \mu_B - \Lambda_B}. \tag{3.5}$$

That is, we obtain

$$\frac{\alpha_T T^* + \mu_I}{\beta M_U^*} = \frac{r}{\gamma_U M_U^* + \mu_B - \Lambda_B}. \tag{3.6}$$

Equation (3.6) implies that

$$M_U^* = \frac{(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U}. \tag{3.7}$$

It is clear that $M_U^* > 0$ when $r\beta - (\alpha_T T^* + \mu_I)\gamma_U > 0$, which implies that

$$T^* < \frac{\mu_I(\mu_B - \Lambda_B)\mathcal{R}_0 + \mu_I\gamma_U(\mathcal{R}_0 - 1)}{\gamma_U\alpha_T} \triangleq T_m. \tag{3.8}$$

On the other hand, $M_U^* \leq 1$ when $T^* \leq \frac{\mu_I}{\alpha_T}(\mathcal{R}_0 - 1)$, which implies that $T^* > 0$ holds if and only if $\mathcal{R}_0 > 1$. That is, $0 < M_U^* \leq 1$ holds when $0 < T^* \leq \frac{\mu_I}{\alpha_T}(\mathcal{R}_0 - 1) \triangleq T_M^*$ and $\mathcal{R}_0 > 1$. Therefore, when $\mathcal{R}_0 > 1$, model (1.2) may exist the bacteria-present equilibrium $P_1 = (M_U^*, M_I^*, B^*, T^*)$ with $T^* < \min\{T_M, T_M^*\} \triangleq \tilde{T}$.

Next, we study the existence and uniqueness of T^* in the interval $(0,\tilde{T})$, which means the existence and uniqueness of the bacteria-present equilibrium P_1 of model (1.2). To this end, taking the expressions of (3.2) and (3.3) into (3.4), we have

$$\mu_U-\mu_U M_U^*=(\alpha_T T^*+\mu_I)\frac{\mu_T T^*}{(1-T^*)k_I}. \tag{3.9}$$

Taking the expressions of (3.7) into (3.9), we have

$$\begin{aligned}&[r\beta-(\alpha_T T^*+\mu_I)\gamma_U][\mu_U(1-T^*)k_I-\mu_T(\alpha_T T^*+\mu_I)T^*]\\&\quad-\mu_U(\alpha_T T^*+\mu_I)(\mu_B-\Lambda_B)(1-T^*)k_I=0.\end{aligned} \tag{3.10}$$

By equation (3.10), we conclude that T^* is the root of the following function $f(T)$ defined by the

$$\begin{aligned}f(T)=&-\mu_T\alpha_T[r\beta-(\alpha_T T+\mu_I)\gamma_U](T^2+\frac{\mu_I\mu_T+\mu_U k_I}{\mu_T\alpha_T}T-\frac{\mu_U k_I}{\mu_T\alpha_T})\\&-\mu_U(\alpha_T T+\mu_I)(\mu_B-\Lambda_B)(1-T)k_I,\quad T\in(0,\tilde{T}).\end{aligned} \tag{3.11}$$

Because of

$$T^2+\frac{\mu_I\mu_T+\mu_U k_I}{\mu_T\alpha_T}T-\frac{\mu_U k_I}{\mu_T\alpha_T}=(T-\xi)(T-\eta), \tag{3.12}$$

where

$$\begin{aligned}\xi&=\frac{-\frac{\mu_I\mu_T+\mu_U k_I}{\mu_T\alpha_T}+\sqrt{(\frac{\mu_I\mu_T+\mu_U k_I}{\mu_T\alpha_T})^2+4\frac{\mu_U k_I}{\mu_T\alpha_T}}}{2}<T_M,\\\eta&=\frac{-\frac{\mu_I\mu_T+\mu_U k_I}{\mu_T\alpha_T}-\sqrt{(\frac{\mu_I\mu_T+\mu_U k_I}{\mu_T\alpha_T})^2+4\frac{\mu_U k_I}{\mu_T\alpha_T}}}{2}<0,\end{aligned} \tag{3.13}$$

(3.11) can be rewritten as

$$\begin{aligned}f(T)=&-\mu_T\alpha_T[r\beta-(\alpha_T T+\mu_I)\gamma_U](T-\xi)(T-\eta)\\&-\mu_U(\alpha_T T+\mu_I)(\mu_B-\Lambda_B)(1-T)k_I,\quad T\in(0,\tilde{T}).\end{aligned} \tag{3.14}$$

Rearranging (3.14), we have

$$f(T)=y_1T^3+y_2T^2+y_3T+y_4,\quad T\in(0,\tilde{T}), \tag{3.15}$$

where

$$\begin{aligned}y_1=&\alpha_T^2\gamma_U\mu_T,\\y_2=&\mu_U\alpha_T k_I(\mu_B-\Lambda_B+\gamma_U)-(r\beta-2\mu_I\gamma_U)\mu_T\alpha_T,\\y_3=&-\mu_U k_I\alpha_T(\mu_B-\Lambda_B+\gamma_U)-\mu_U k_I\mu_I(\mu_B\\&-\Lambda_B+\gamma_U)(\mathcal{R}_0-1)-\mu_I\mu_T(r\beta-\mu_I\gamma_U),\\y_4=&\mu_I\mu_U k_I(\gamma_U+\mu_B-\Lambda_B)(\mathcal{R}_0-1).\end{aligned}$$

It is clear that $y_1>0$, and $f(0)=y_4>0$ when $\mathcal{R}_0>1$. Since $f(\xi)=-\mu_U(\alpha_T\xi+\mu_I)(\mu_B-\Lambda_B)(1-\xi)k_I<0$, and $\xi>0$, we know $f(T)=0$ has one negative root and two positive roots.

In order to ensure the existence of the bacteria-present equilibrium P_1 of model (1.2), we only need to discuss the positive root of $f(T)=0$ in the interval $(0,\tilde{T})$.

When $T_M < T_M^* < T_m$, we have

$$\begin{aligned} r\beta - (\alpha_T T_M + \mu_I)\gamma_U &> r\beta - (\alpha_T T_M^* + \mu_I)\gamma_U \\ &> r\beta - (\alpha_T T_m + \mu_I)\gamma_U \\ &= 0. \end{aligned}$$

Thus,

$$\begin{aligned} f(T_M) = &- \mu_T\alpha_T[r\beta - (\alpha_T T_M + \mu_I)\gamma_U](T_M - \xi)(T_M - \eta) \\ &- \mu_U(\alpha_T T_M + \mu_I)(\mu_B - \Lambda_B)(1 - T_M)k_I < 0. \end{aligned}$$

When $T_M^* < T_M$, we have

$$(\alpha_T T_M^* + \mu_I)(\mu_B - \Lambda_B) = r\beta - (\alpha_T T_M^* + \mu_I)\gamma_U.$$

Thus,

$$\begin{aligned} f(T_M^*) = &- \mu_T\alpha_T[r\beta - (\alpha_T T_M^* + \mu_I)\gamma_U][T_M^{*2} + \frac{\mu_I\mu_T + \mu_U k_I}{\mu_T\alpha_T}T_M^* - \frac{\mu_U k_I}{\mu_T\alpha_T}] \\ &- \mu_U(\alpha_T T_M^* + \mu_I)(\mu_B - \Lambda_B)(1 - T_M^*)k_I \\ = &- (\alpha_T T_M^* + \mu_I)(\mu_B - \Lambda_B)(\mu_T\alpha_T T_M^{*2} + \mu_I\mu_T T_M^*) < 0. \end{aligned}$$

Therefore, when $\mathcal{R}_0 > 1$, $f(T) = 0$ has the unique positive roots T^* in the interval $(0, \tilde{T})$. That is, model (1.2) has the unique bacteria-present equilibrium P_1.

Summarizing the above analysis, we have the following result:

Theorem 3.1. *Model* (1.2) *always has the bacterium-free equilibrium* $P_0 = (1, 0, 0, 0)$. *In addition, if* $\mathcal{R}_0 > 1$, *model* (1.2) *also has the unique the bacteria-present equilibrium* $P_1 = (M_U^*, M_I^*, B^*, T^*)$, *where*

$$M_I^* = \frac{\mu_T T^*}{(1 - T^*)k_I},\ B^* = \frac{\mu_U - \mu_U M_U^*}{\beta M_U^*},\ M_U^* = \frac{(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U},$$

and T^* *is the solution of* $f(T) = 0$ *in* (3.15).

4. Global analysis

In this section, we focus on the stability of the bacterium-free equilibrium P_0 and the bacteria-present equilibrium P_1.

Theorem 4.1. *If* $\mathcal{R}_0 < 1$, *the bacterium-free equilibrium* P_0 *is globally asymptotically stable, while if* $\mathcal{R}_0 > 1$, *the bacterium-free equilibrium* P_0 *is unstable.*

Proof. The Jacobian matrix of model (1.2) at P_0

$$J(P_0) = \begin{pmatrix} -\mu_U & 0 & -\beta & 0 \\ 0 & -\mu_I & \beta & 0 \\ 0 & r & -(\gamma_U + \mu_B) + \Lambda_B & 0 \\ 0 & k_I & 0 & -\mu_T \end{pmatrix}.$$

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Therefore, the characteristic equation of the system (1.2) at P_0 is

$$\begin{aligned} p_1(\lambda) &= (\lambda+\mu_U)[(\lambda+\mu_I)(\lambda+(\gamma_U+\mu_B)-\Lambda_B)(\lambda+\mu_T)-r\beta(\lambda+\mu_T)] \\ &= (\lambda+\mu_U)(\lambda+\mu_T)[\lambda^2+(\gamma_U+\mu_B-\Lambda_B+\mu_I)\lambda+\mu_I(\gamma_U+\mu_B-\Lambda_B)-r\beta]. \end{aligned}$$

It is clear that both $\lambda_1=-\mu_U$ and $\lambda_2=-\mu_T$ are the characteristic roots, and the remaining characteristic roots satisfy

$$g(\lambda)=\lambda^2+(\frac{r\beta}{\mathcal{R}_0\mu_I}+\mu_I)\lambda+(\frac{1}{\mathcal{R}_0}-1)r\beta=0. \tag{4.1}$$

Because $\frac{r\beta}{\mathcal{R}_0\mu_I}+\mu_I>0$, we know $g(\lambda)=0$ has one positive real root if $\mathcal{R}_0>1$, which implies that P_0 is unstable. While if $\mathcal{R}_0<1$, the Routh-Hurwitz criterion implies that the roots of $g(\lambda)=0$ 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

$$V_0=rM_I+\mu_I B.$$

When $\mathcal{R}_0<1$, $r\beta-\gamma_U\mu_I<\mu_I(\mu_B-\Lambda_B)$. Then, we have

$$\begin{aligned} \frac{dV_0}{dt} &= r(\beta BM_U-\alpha_T M_I T-\mu_I M_I)+\mu_I(\Lambda_B B+rM_I-\gamma_U M_U B-\mu_B B) \\ &= BM_U(r\beta-\gamma_U\mu_I)-r\alpha_T M_I T+\mu_I B(\Lambda_B-\mu_B) \\ &< BM_U\mu_I(\mu_B-\Lambda_B)-r\alpha_T M_I T-\mu_I B(\mu_B-\Lambda_B) \\ &= B\mu_I(\mu_B-\Lambda_B)(M_U-1)-r\alpha_T M_I T. \end{aligned} \tag{4.2}$$

Because $\mu_B>\Lambda_B$, $M_U<1$, thus, when $\mathcal{R}_0<1$, for all $x\in\Omega$, $V_0'(x)\le 0$. 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_1 is locally asymptotically stable.*

Proof. The Jacobian matrix of model (1.2) at the bacteria-present equilibrium P_1 is:

$$J(P_1)=\begin{pmatrix} -\mu_U-\beta B^* & 0 & -\beta M_U^* & 0 \\ \beta B^* & -\alpha_T T^*-\mu_I & \beta M_U^* & -\alpha_T M_I^* \\ -\gamma_U B^* & r & \Lambda_B-\gamma_U M_U^*-\mu_B & 0 \\ 0 & (1-T^*)k_I & 0 & -k_I M_I^*-\mu_T \end{pmatrix}.$$

Therefore, the characteristic equation of matrix $J(P_1)$ is

$$p_2(\lambda)=\lambda^4+c_1\lambda^3+c_2\lambda^2+c_3\lambda+c_4, \tag{4.3}$$

where

$$\begin{aligned}
c_1 =&\mu_U + \beta B^* + \alpha_T T^* + \mu_I + \mu_B - \Lambda_B + \gamma_U M_U^* + k_I M_I^* + \mu_T,\\
c_2 =&(\mu_U + \beta B^*)(\alpha_T T^* + \mu_I) + (\mu_U + \beta B^* + \alpha_T T^* + \mu_I)(\mu_B - \Lambda_B + \gamma_U M_U^*)\\
&+ (k_I M_I^* + \mu_T)(\mu_U + \beta B^* + \alpha_T T^* + \mu_I + \mu_B - \Lambda_B + \gamma_U M_U^*)\\
&+ \alpha_T M_I^*(1 - T^*)k_I - r\beta M_U^* - \beta M_U^* \gamma_U B^*,\\
c_3 =&(\mu_U + \beta B^*)(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B + \gamma_U M_U^*)\\
&+ (k_I M_I^* + \mu_T)[(\mu_U + \beta B^*)(\alpha_T T^* + \mu_I)\\
&+ (\mu_U + \beta B^* + \alpha_T T^* + \mu_I)(\mu_B - \Lambda_B + \gamma_U M_U^*)]\\
&+ (\mu_U + \beta B^* + \mu_B - \Lambda_B + \gamma_U M_U^*)\alpha_T M_I^*(1 - T^*)k_I + r\beta B^* \beta M_U^*\\
&- r\beta M_U^*(\mu_U + \beta B^* + k_I M_I^* + \mu_T) - \beta M_U^* \gamma_U B^*(\alpha_T T^* + \mu_I + k_I M_I^* + \mu_T),\\
c_4 =&(\mu_U + \beta B^*)(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B + \gamma_U M_U^*)(k_I M_I^* + \mu_T)\\
&+ (\mu_U + \beta B^*)(\mu_B - \Lambda_B + \gamma_U M_U^*)\alpha_T M_I^*(1 - T^*)k_I\\
&+ r\beta B^* \beta M_U^*(k_I M_I^* + \mu_T) - r\beta M_U^*(\mu_U + \beta B^*)(k_I M_I^* + \mu_T)\\
&- \beta M_U^* \gamma_U B^* \alpha_T M_I^*(1 - T^*)k_I - \beta M_U^* \gamma_U B^*(\alpha_T T^* + \mu_I)(k_I M_I^* + \mu_T).
\end{aligned} \tag{4.4}$$

By substituting M_U^*, M_I^* and B^* from Theorem 3.1 into (4.4), we have

$$\begin{aligned}
c_1 =&\frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)} + \alpha_T T^* + \mu_I + \mu_B - \Lambda_B\\
&+ \frac{\gamma_U(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U} + \frac{\mu_T}{1 - T^*},\\
c_2 =&\frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{\mu_B - \Lambda_B} + \frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{\alpha_T T^* + \mu_I}\\
&+ \frac{\mu_T}{1 - T^*}\left(\frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)} + \alpha_T T^* + \mu_I + \mu_B - \Lambda_B\right.\\
&\left.+\frac{\gamma_U(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U}\right) + \alpha_T \mu_T T^* + \frac{\mu_U \gamma_U(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U},\\
c_3 =&\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U - (\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)]\\
&+ \frac{\mu_T}{1 - T^*}\frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{\mu_B - \Lambda_B} + \frac{\mu_T}{1 - T^*}\frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{\alpha_T T^* + \mu_I}\\
&+ \left(\frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)} + \mu_B - \Lambda_B + \frac{\gamma_U(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U}\right)\\
&\alpha_T \mu_T T^* + \frac{\mu_U \gamma_U(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U}\frac{\mu_T}{1 - T^*},\\
c_4 =&\frac{\mu_T}{1 - T^*}\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U - (\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)]\\
&+ \frac{\mu_U[r\beta - (\alpha_T T^* + \mu_I)\gamma_U]}{\alpha_T T^* + \mu_I}\alpha_T \mu_T T^* + \frac{\mu_U \gamma_U(\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)}{r\beta - (\alpha_T T^* + \mu_I)\gamma_U}\alpha_T \mu_T T^*.
\end{aligned} \tag{4.5}$$

Since $r\beta - (\alpha_T T^* + \mu_I)\gamma_U > 0$, $\mu_B - \Lambda_B > 0$, $1 - T^* > 0$, and according to (3.10), we have

$$\begin{aligned}
&u_U(1 - T^*)k_I[r\beta - (\alpha_T T^* + \mu_I)\gamma_U - (\alpha_T T^* + \mu_I)(\mu_B - \Lambda_B)]\\
&\qquad = [r\beta - (\alpha_T T^* + \mu_I)\gamma_U]\mu_T(\alpha_T T^* + \mu_I)T^*.
\end{aligned}$$

Then $r\beta-(\alpha_T T^*+\mu_I)\gamma_U-(\alpha_T T^*+\mu_I)(\mu_B-\Lambda_B)>0$.

It follows from the Routh-Hurwitz criterion that the roots of the polynomial $p_1(\lambda)$ has a negative real part if and only if its coefficients satisfy (4.6), thus the bacteria-present equilibrium is locally asymptotically stable.

$$\begin{aligned} &c_1>0, c_2>0, c_3>0, c_4>0,\\ &D_1=c_1>0,\\ &D_2=c_1c_2-c_3>0,\\ &D_3=(c_1c_2-c_3)c_3-c_1^2c_4>0. \end{aligned} \tag{4.6}$$

It is clear that $c_1, c_2, c_3, c_4>0$. For easy writing, we make

$$\begin{aligned} &A=r\beta-(\alpha_T T^*+\mu_I)\gamma_U, \quad C=\alpha_T T^*+\mu_I,\\ &D=\mu_B-\Lambda_B, \quad E=\frac{\mu_T}{1-T^*}, \quad F=\alpha_T\mu_T T^*. \end{aligned} \tag{4.7}$$

After simplification, D_2, D_3 can be written as

$$\begin{aligned} D_2 =&(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A})[\frac{\mu_U A}{D}+\frac{\mu_U A}{C}+E(\frac{\mu_U A}{CD})+C+D+\frac{\gamma_U CD}{A})+\frac{\mu_U\gamma_U CD}{A}]\\ &+C[\frac{\mu_U A}{D}+\frac{\mu_U A}{C}+E(C+D+\frac{\gamma_U CD}{A})+F+\frac{\mu_U\gamma_U CD}{A}]\\ &+D[\frac{\mu_U A}{C}+E(C+D+\frac{\gamma_U CD}{A})+\frac{\mu_U\gamma_U CD}{A}]\\ &+E[\frac{\mu_U A}{D}+\frac{\mu_U A}{C}+E(\frac{\mu_U A}{CD}+C+D+\frac{\gamma_U CD}{A})+F]+\mu_U CD,\\ D_3 =&\gamma_U\mu_U C(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A})F(1-\frac{CD}{A})\\ &+\gamma_U\mu_U C[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U\gamma_U CD}{A}E]\\ &+\frac{\mu_U A}{CD}\frac{\mu_U A}{D}[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A})F\\ &+\frac{\mu_U\gamma_U CD}{A}E]+(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A})\frac{\mu_U A}{C}[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}\\ &+\frac{\mu_U\gamma_U CD}{A}E]+\frac{\mu_U A}{CD}E\gamma_U\mu_U F(1-\frac{CD}{A})+\mu_U\gamma_U EDF(1-\frac{CD}{A})\\ &+\mu_U\gamma_U E(E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\gamma_U CD}{A}F+\frac{\mu_U\gamma_U CD}{A}E)\\ &+\frac{\mu_U A}{CD}E\mu_U\gamma_U F(1-\frac{CD}{A})+\frac{\mu_U A}{CD}E\frac{\mu_U A}{CD}[E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+D)F\\ &+\frac{\mu_U\gamma_U CD}{A}E]+\frac{\mu_U A}{CD}ED(E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U\gamma_U CD}{A}E)\\ &+\mu_U\gamma_U EDF(1-\frac{CD}{A})+\frac{\mu_U A}{CD}EC(E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U A}{CD}F\\ &+\frac{\gamma_U CD}{A}E\frac{\gamma_U CD}{A}[E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(D+\frac{\gamma_U CD}{A})F+\frac{\mu_U\gamma_U CD}{A}E]\\ &+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F+\frac{\mu_U\gamma_U CD}{A}E]\\ &+\frac{\mu_U\gamma_U CD}{A}E)+\mu_U\gamma_U ECF(1-\frac{CD}{A})+\frac{\gamma_U CD}{A}E\gamma_U\mu_U F(1-\frac{CD}{A}) \end{aligned}$$

$$
\begin{aligned}
&+\frac{\gamma_U CD}{A}E\frac{\mu_U A}{CD}(E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U A}{CD}F+\frac{\mu_U\gamma_U CD}{A}E)\\
&+\frac{\gamma_U CD}{A}E\mu_U\gamma_U F(1-\frac{CD}{A})+\frac{\gamma_U CD}{A}ED[E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F\\
&+\frac{\mu_U\gamma_U CD}{A}E]+E\frac{\gamma_U CD}{A}ECD+\frac{\gamma_U CD}{A}EC[E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}\\
&+(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A})\frac{\mu_U\gamma_U CD}{A}[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U\gamma_U CD}{A}E]\\
&+CF[\mu_U(A-CD)+E\frac{\mu_U A}{D}+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F]\\
&+E^2C[E\frac{\mu_U A}{D}+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F+\frac{\mu_U\gamma_U CD}{A}E]+E^3CD\\
&+E^2D[E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F+\frac{\mu_U\gamma_U CD}{A}E]\\
&+C\frac{\mu_U A}{D}[\mu_U(A-CD)+\frac{\mu_U A}{CD}F+E\frac{\mu_U A}{D}+\frac{\mu_U\gamma_U CD}{A}E]\\
&+C\frac{\mu_U A}{CD}ECD+C^2\mu_U\gamma_U F(1-\frac{CD}{A})+C^2DE^2\\
&+CE(C+D+\frac{\gamma_U CD}{A})[E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F+\frac{\gamma_U\mu_U CD}{A}E]\\
&+D^2E[E\frac{\mu_U A}{C}+\frac{\gamma_U\mu_U CD}{A}E+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F]+CD^2E^2\\
&+D\frac{\mu_U A}{C}[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U\gamma_U CD}{A}E]\\
&+CDE[E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+D+\frac{\gamma_U CD}{A})F+\frac{\mu_U\gamma_U CD}{A}E]\\
&+D\frac{\mu_U\gamma_U CD}{A}[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U\gamma_U CD}{A}E]\\
&+\mu_U CD[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+D)F+\frac{\mu_U\gamma_U CD}{A}E]\\
&+[D(E\frac{\gamma_U CD}{A})+E(\frac{\mu_U A}{D}+EF)][E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A}\\
&+D)F+\frac{\mu_U\gamma_U CD}{A}E]+DE(\frac{\mu_U A}{D}+EF)\mu_U(A-CD)+\mu_U A[\mu_U(A-CD)\\
&+E\frac{\mu_U A}{D}+\frac{\mu_U\gamma_U CD}{A}E]+D\frac{\mu_U\gamma_U CD}{A}[\mu_U(A-CD)+E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}\\
&+\frac{\mu_U\gamma_U CD}{A}E]+E^2\frac{\mu_U A}{CD}(E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+\frac{\mu_U A}{CD}F+\frac{\mu_U\gamma_U CD}{A}E)\\
&+E^2\mu_U\gamma_U F(1-\frac{CD}{A})+E^2\frac{\gamma_U CD}{A}[E\frac{\mu_U A}{D}+E\frac{\mu_U A}{C}+(\frac{\mu_U A}{CD}+\frac{\gamma_U CD}{A}\\
&+D)F+\frac{\mu_U\gamma_{UCD}}{A}E]+E\frac{\mu_U A}{C}\mu_U[(A-CD)+E\frac{\mu_U A}{C}+\frac{\mu_U\gamma_U CD}{A}E]\\
&+E^2\mu_U A+CE(C+\frac{\gamma_U CD}{A})E\frac{\mu_U A}{D}\\
&+E\mu_U A(ET^*+\mu_T+\alpha_T M_I^* T^* k_I+E\mu_I),
\end{aligned}
$$

Because

$$A-CD=r\beta-(\alpha_T T^*+\mu_I)\gamma_U-(\alpha_T T^*+\mu_I)(\mu_B-\Lambda_B)>0,$$

it is clear that when $\mathcal{R}_0 > 1$, $D_2 > 0$, $D_3 > 0$. That is, the bacteria-present equilibrium P_1 is locally asymptotically stable when $\mathcal{R}_0 > 1$. □

Theorem 4.3. *If $\mathcal{R}_0 > 1$, and $B^* \leq \frac{\mu_U(\mu_B-\Lambda_B)}{\beta M_U^* \gamma_U}$, then the bacteria-present equilibrium P_1 is globally asymptotically stable.*

Proof. We will prove the global stability of P_1 by constructing a Lyapunov function. Let

$$\begin{aligned} V_1 =&(a_1+a_2)[M_U - M_U^* - M_U^* \ln(\frac{M_U}{M_U^*})] + (a_3+a_4)[M_I - M_I^* - M_I^* \ln(\frac{M_I}{M_I^*})] \\ &+ a_5[B - B^* - B^* \ln(\frac{B}{B^*})] + a_6[T - T^* - T^* \ln(\frac{T}{T^*})], \end{aligned} \tag{4.8}$$

where

$$\begin{aligned} &a_1 = \beta B^* M_U^* \gamma_U,\ a_2 = \mu_U(\mu_B - \Lambda_B) - \beta B^* M_U^* \gamma_U,\ a_3 = \mu_U(\mu_B - \Lambda_B), \\ &a_4 = \mu_U M_U^* \gamma_U,\ a_5 = \mu_U M_U^* \beta,\ a_6 = \frac{[\mu_U M_U^* \gamma_U + \mu_U(\mu_B - \Lambda_B)]\alpha_T T^* M_I^*}{k_I M_I^*(1-T^*)}. \end{aligned} \tag{4.9}$$

It is clear that $V_1(x) > 0$, and $V_1(P_1) = 0$ for $x \in \Omega$. Then, taking the derivative of V_1 directly yields that

$$\begin{aligned} \frac{dV_1}{dt} =&(a_1+a_2)(M_U - M_U^*)(\frac{\mu_U}{M_U} - \mu_U - \beta B) \\ &+ (a_3+a_4)(M_I - M_I^*)(\frac{\beta B M_U}{M_I} - \alpha_T T - \mu_I) \\ &+ a_5(B - B^*)(\Lambda_B + \frac{rM_I}{B} - \gamma_U M_U - \mu_B) \\ &+ a_6(T - T^*)(\frac{k_I M_I}{T} - k_I M_I - \mu_T). \end{aligned} \tag{4.10}$$

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

$$\begin{aligned} &\mu_U = \mu_U M_U^* + \beta B^* M_U^*,\ \mu_I = \frac{\beta B^* M_U^*}{M_I^*} - \frac{\alpha_T T^* M_I^*}{M_I^*}, \\ &\mu_B = \frac{rM_I^*}{B^*} - \gamma_U M_U^* + \Lambda_B,\ \mu_T = \frac{k_I M_I^*}{T^*} - k_I M_I^*. \end{aligned} \tag{4.11}$$

Taking (4.11) into (4.10), we can get

$$\begin{aligned} \frac{dV_1}{dt} =&(a_1+a_2)[\mu_U M_U^*(2 - \frac{M_U^*}{M_U} - \frac{M_U}{M_U^*}) + \beta B^* M_U^*(1 + \frac{B}{B^*} - \frac{M_U^*}{M_U} - \frac{BM_U}{B^* M_U^*})] \\ &+ (a_3+a_4)[\beta B^* M_U^*(\frac{BM_U}{B^* M_U^*} - \frac{BM_U M_I^*}{B^* M_U^* M_I} - \frac{M_I}{M_I^*} + 1) \\ &+ \alpha_T T^* M_I^*(\frac{T}{T^*} + \frac{M_I}{M_I^*} - \frac{TM_I}{T^* M_I^*} - 1)] \\ &+ a_5[rM_I^*(\frac{M_I}{M_I^*} + 1 - \frac{M_I B^*}{M_I^* B} - \frac{B}{B^*}) + \gamma_U M_U^* B^*(\frac{M_U}{M_U^*} + \frac{B}{B^*} - 1 - \frac{M_U B}{M_U^* B^*})] \\ &+ a_6[k_I M_I^*(\frac{M_I}{M_I^*} - \frac{M_I T^*}{M_I^* T} - \frac{T}{T^*} + 1) \\ &+ k_I M_I^* T^*(-\frac{M_I T}{M_I^* T^*} + \frac{M_I}{M_I^*} + \frac{T}{T^*} - 1)]. \end{aligned}$$

Denoting $h = \frac{M_U}{M_U^*}$, $y = \frac{M_I}{M_I^*}$, $z = \frac{B}{B^*}$, and $w = \frac{T}{T^*}$, we have

$$\begin{aligned}\frac{dV_1}{dt} =&(a_1+a_2)[\mu_U M_U^*(2-\frac{1}{h}-h)+\beta B^* M_U^*(1+z-\frac{1}{h}-hz)]\\ &+(a_3+a_4)[\beta B^* M_U^*(zh-\frac{zh}{y}-y+1)+\alpha_T T^* M_I^*(w+y-wy-1)]\\ &+a_5[rM_I^*(y+1-\frac{y}{z}-z)+\gamma_U M_U^* B^*(h+z-1-hz)]\\ &+a_6[k_I M_I^*(y-\frac{y}{w}-w+1)+k_I M_I^* T^*(-yw+y+w-1)].\end{aligned} \tag{4.12}$$

Furthermore, by using

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

(4.12) can be rewritten as

$$\begin{aligned}\frac{dV_1}{dt} =&(a_3+a_4)\beta B^* M_U^*(3-\frac{hz}{y}-\frac{y}{z}-\frac{1}{h})+a_2\mu_U M_U^*(2-h-\frac{1}{h})\\ &+a_6 k_I M_I^* y(2-w-\frac{1}{w}).\end{aligned}$$

Obviously, $a_i > 0$, $i = 1,3,4,5,6$, in (4.9). In addition, $B^* \le \frac{\mu_U(\mu_B-\Lambda_B)}{\beta M_U^*\gamma_U}$ can ensure $a_2 \ge 0$. Therefore, we can get $\frac{dV_1}{dt}(x) \le 0$ for any $x \in \Omega$, and $\frac{dV_1}{dt}(x) = 0$ if and only if $x = P_1$. That is, the LaSalle-Lyapunov Theorem implies that P_1 is globally asymptotically stable in $\mathcal{R}_0 > 1$ and $B^* \le \frac{\mu_U(\mu_B-\Lambda_B)}{\beta M_U^*\gamma_U}$. This means that at $\mathcal{R}_0 > 1$, if $B \in (0, \frac{\mu_U(\mu_B-\Lambda_B)}{\beta M_U^*\gamma_U}]$, then the bacteria-present equilibrium P_1 is globally asymptotically stable, and at this time bacterial growth is controlled, which is the latent period of TB; and if $B > \frac{\mu_U(\mu_B-\Lambda_B)}{\beta M_U^*\gamma_U}$, then the bacteria-present equilibrium P_1 is unstable, and at this time bacterial growth is not controlled, and is active TB. □

5. The sensitivity analysis and numerical simulations

Some individuals infected with Mtb can eliminate or control the infection, thus remain in a latent state, while others can develop active disease in the short or long term. Identifying the immune mechanisms that determine whether an infected individual will suffer from active or latent TB can help in the development of treatment and prevention strategies. We will choose five parameters related to $\bar{M}_I$ and $\bar{B}$, that is, $\bar{\beta}$, $\bar{\alpha_T}$, $\bar{\gamma}_U$, Λ_B and $\bar{r}$, and use sensitivity analyses based on Latin Hypercube Sampling (LHS) on them, so as to show the effects of these parameters on Mtb in the hosts. The parameter ranges of model (1.1) are put in Table 1. According to the original data, the basic reproduction number of model (1.1) is

$$\mathcal{R}_0 = \frac{\bar{r}\bar{\beta}\Lambda_U}{\bar{\gamma}_U\Lambda_U + \mu_U\mu_B - \Lambda_B\mu_U}.$$

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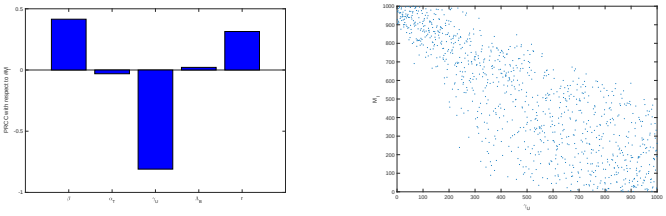
Table 1. Parameter values

Parameter	Value	Unit	Reference
$\bar{\alpha}_T$	$1 \times 10^{-5} - 5 \times 10^{-5}$	day^{-1}	[5]
$\bar{\gamma}_U$	$0.5 \times 10^{-7} - 1.9 \times 10^{-6}$	day^{-1}	Estimate
μ_I	0.011	day^{-1}	[3]
μ_U	0.0028	day^{-1}	[3]
μ_T	0.33	day^{-1}	[3]
μ_B	0.012	day^{-1}	[3]
$\bar{r}$	0.2-0.5	day^{-1}	[5]
Λ_B	0-0.011	day^{-1}	[9]
Λ_U	1000	$1/ml \quad day$	[3]
$\bar{\beta}$	$1 \times 10^{-6} - 3 \times 10^{-6}$	day^{-1}	[5]
$\bar{k}_I$	0.008	day^{-1}	[3]
T_{max}	50000	day^{-1}	[3]

Both Fig.1 and Fig.2 show that the rate at which activated infected macrophages kill Mtb $\bar{\gamma}_U$ has the greatest effect on infected macrophages and Mtb, followed by the infection rate $\bar{\beta}$ of activated infected macrophages and the average number $\bar{r}$ of bacteria released by apoptosis of infected macrophages. This means that if the ability of activated infected macrophages to kill Mtb is weakened, Mtb will increase substantially in the host. In other words, the immune system of an infected person determines whether Mtb is cleared from the body, develops latent TB, or progresses to active TB.



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

Figure 1. The sensitivity analysis of M_I on part parameter.

In the following, we will simulate different outcomes of the disease. First simulate the state where Mtb invading the host is eliminated. Take the parameters $\bar{\alpha}_T = 3 \times 10^{-5}$, $\bar{\gamma}_U = 3 \times 10^{-7}$, $\mu_I = 0.011$, $\mu_U = 0.0028$, $\mu_T = 0.33$, $\mu_B = 0.012$, $\bar{\beta} = 1 \times 10^{-6}$, $\bar{r} = 0.2$, $\bar{k_I} = 0.008$, $\Lambda_U = 1000$, $\Lambda_B = 0.011$, and $T_{max} = 50000$. At this stage with $\mathcal{R}_0 = 0.6605$, the simulation results for this case are shown in the following Fig.3. Fig.3 shows that the number of activated infected macrophages increases substantially over time, while the number of Mtb, infected macrophages and T cells decreases to zero. In other words, Mtb is removed from the human

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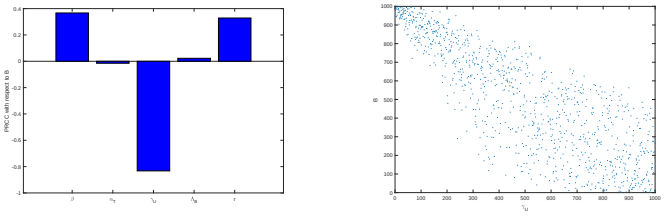

(a) The sensitivity analysis (b) The scatter plots

Figure 2. The sensitivity analysis of B on part parameter.

body, so the infected individuals is not infected and is healthy.

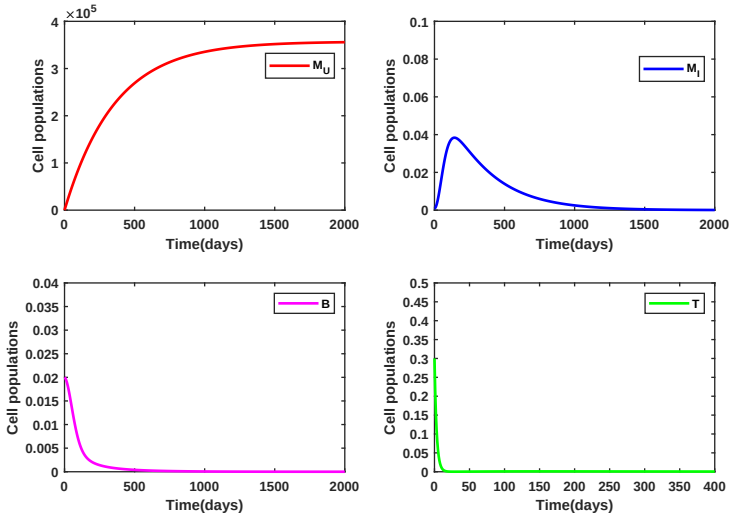

Figure 3. The uninfected stage is formed after Mtb invades the host when $\mathcal{R}_0 < 1$.

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Then, we simulate the latent infection formed by Mtb entering the human body. Take the parameters $\bar{\gamma}_U = 1.9\times10^{-7}$, and keep the other parameters consistent with Fig.3. At this stage $\mathcal{R}_0 = 1.0373$, and the simulation results for this case are shown in the following Fig.4. Fig.4 shows that over time, the number of activated infected macrophages grows substantially and T cells decrease to zero. Although Mtb and infected macrophages are eventually present in the body, the number of activated infected macrophages is much greater than the number of infected macrophages and Mtb, which is the latent period of TB. During the latent period, infected individuals are not contagious and do not show obvious symptoms, but they should pay attention to their immunity and avoid prolonged fatigue and malnutrition. If the immune system is weakened, it may lead to reactivation of the disease and the development of active TB. It is important for infected individuals to be exercised and to have regular checkups at the hospital.

At last, we simulate the state of active TB in which Mtb invades the host. Take

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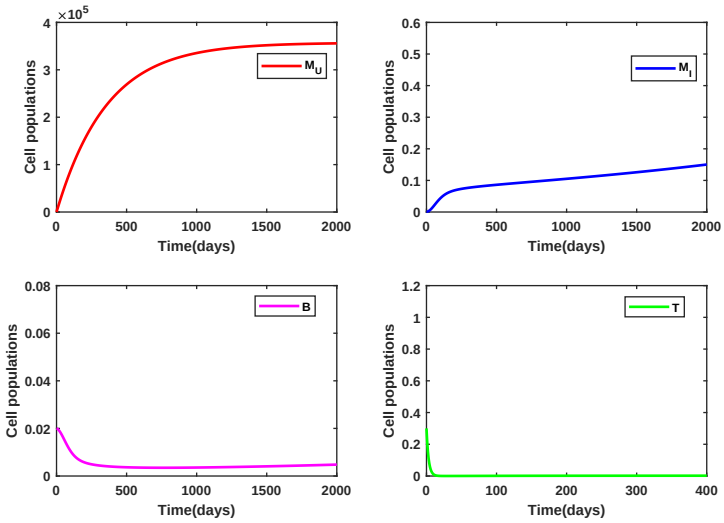

Figure 4. The latent stage is formed after Mtb invades the host when $\mathcal{R}_0 > 1$.

the parameters $\bar{r} = 0.5$, $\bar{\beta}_T = 2 \times 10^{-6}$, $\bar{\gamma}_U = 1.2 \times 10^{-7}$, and keep the other parameters consistent with Fig.3. At this time $\mathcal{R}_0 = 8.1433$, and the simulation results for this case are shown in the following Fig.5. Fig.5 shows that activated infected macrophages grow rapidly during the initial phase of infection, followed by a rapid growth of T cells and infected macrophages, then infected macrophages decrease dramatically due to the burst, which results in the release of a large number of bacteria, and these bacteria multiply so that the bacterial population grows beyond the control of the immune cells. This is a state of active infection, leading to uncontrolled infection and eventual development of active TB. At this time, the individual is contagious and clearly symptomatic.

6. Conclusion

Based on the immune response after Mtb invasion, we developed a mathematical model of in-host TB granuloma. For this model, we demonstrate the existence and the global stability of the bacteria-free equilibrium and the bacteria-present equilibrium, then perform sensitivity analyses on important parameters. Finally, three different states of Mtb after entering the host are numerically simulated. The main objective is to analyze the changes in the number of infected macrophages and Mtb after the entry of Mtb into the host, and to find out the immune mechanism that determines whether an infected individual will suffer from active or latent TB.

The results show that when $\mathcal{R}_0 < 1$, the rate $\bar{\gamma}_U$ at which activated infected macrophages kill Mtb is greater, and therefore the number of bacteria is less. When the number of bacteria is small, a large increase in the number of activated infected macrophages will kill the bacteria directly. At this point the individual is not infected and the body is healthy. When $\mathcal{R}_0 > 1$, the rate $\bar{\gamma}_U$ becomes smaller, so the number of surviving bacteria becomes larger. Since $\bar{\gamma}_U$ can still control the number of bacteria at this time, fewer macrophages are infected. Although the

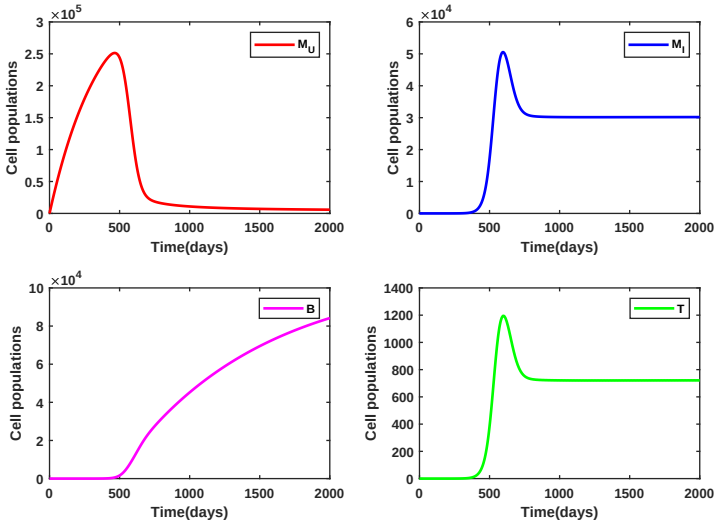

Figure 5. The active stage is formed after Mtb invades the host when $\mathcal{R}_0 > 1$.

individual cannot eliminate Mtb, the number of activated infected macrophages is much greater than the number of Mtb, which is the latent period of TB, i.e., latent infection. Individuals with latent infection are not contagious and do not show obvious symptoms. When the body is chronically tired, malnourished, and immunocompromised, the ability of the activated infected macrophages to kill Mtb is reduced, thus the number od infected macrophages increases, and eventually the bacteria grow in large numbers without being controlled by the immune cells, resulting in an uncontrolled infection that progresses to active TB. At this point, the individual has TB, which is contagious and accompanied by obvious symptoms. In conclusion, the immune system of TB patients, especially the ability of activated infected macrophages to kill Mtb, is related to the treatment and prevention, so it is necessary to strengthen the exercise in daily life and go to the hospital for regular medical checkups.

References [5] proposed that Mtb can also activate T cells. Therefore, a mathematical model of TB granuloma that includes these cells should be considered for our future studies.

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