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A MATHEMATICAL MODEL FOR CELLULAR IMMUNOLOGY OF TUBERCULOSIS

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Abstract. Tuberculosis (TB) is a global emergency. The World Health Organization reports about 9.2 million new infections each year, with an average of 1.7 million people killed by the disease. The causative agent is *Mycobacterium tuberculosis* (Mtb), whose main target are the macrophages, important immune system cells. Macrophages and T cell populations are the main responsible for fighting the pathogen. A better understanding of the interaction between Mtb, macrophages and T cells will contribute to the design of strategies to control TB. The purpose of this study is to evaluate the impact of the response of T cells and macrophages in the control of Mtb. To this end, we propose a system of ordinary differential equations to model the interaction among non-infected macrophages, infected macrophages, T cells and Mtb bacilli. Model analysis reveals the existence of two equilibrium states, infection-free equilibrium and the endemically infected equilibrium which can represent a state of latent or active infection, depending on the amount of bacteria.

1. **Introduction.** Tuberculosis (TB) is an infectious disease whose etiological agent is *Mycobacterium tuberculosis* (Mtb). The World Health Organization (WHO) reports 9.2 million new cases and 1.7 million death each year [18, 13]. However, only 10% of infected individuals with Mtb develop the disease in their lifetime [4]. This indicates that in most cases the host immune system is able to control replication of the pathogen.

The Mtb bacteria may affect different tissues, but usually develop pulmonary TB. After the entrance of the bacilli into the lung, phagocytosis of the bacteria by alveolar macrophages takes place. Cell mediated immune response develops within 2 to 6 weeks, this leads to the activation and recruitment of other immune cell

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populations, such as $CD4^+T$ or $CD8^+T$ lymphocytes. These cells secrete cytokines that help to kill the infected macrophages [7].

The specific immune response to Mtb results in the formation of granulomas at the site of bacteria implantation. A granuloma is an spherical structure composed of bacteria, macrophages, and other immune cells. One of its characteristic is the formation of a caseous (cheese-like appearance) center containing necrotic tissue, cellular detritus and dead Mtb. The vital dynamics of bacteria takes place inside the granuloma, which can support a population of bacteria that frequently exceeds 10^9. Bacilli are then contained in the granuloma, where they can remain forever or be reactivated later after increasing to a limit in which the macrophages burst, releasing more bacteria [17]. In most cases the initial infection progresses to a latent form which can be maintained for the lifetime of the host with no clinical symptoms. The reactivation of the latent infection can be due to aging, malnutrition, infection with HIV, and other factors.

The difference between latent and active infection is diagnosed in terms of the clinical manifestations of TB. A person with latent TB usually has a skin or blood test result indicating Mtb infection; normal chest x-ray and negative sputum test; Mtb bacteria in the body are alive but inactive; he or she does not feel sick and can not spread Mtb bacteria to others. On the other hand, active disease has the following symptoms: a skin test or blood test result indicating TB; may have an abnormal chest x-ray, or positive sputum smear or culture; has active Mtb bacteria in his/her body; the person usually feels sick and may have symptoms such as coughing, fever and weight loss; may spread Mtb bacteria to others [3].

Although the definitions above are not given in terms of bacilli's number, it is reasonable to think that if this number is very large, the bacteria can be found in the sputum, skin, peripheral lymph nodes, kidneys, brain, or bones implying that TB infection is active. Is worth mentioning that in any case the bacteria will primarily be inside the granulomas.

It is believed that granulomas are advantageous to the host since they contain and restrict mycobacteria [17]. However, recent studies in zebrafish infected with *Mycobacterium marinum* suggest that granulomas contribute to early bacterial growth, and protect Mtb bacteria from the immune system [12].

The immune response following the first exposure to Mtb is multifaceted and complex. Animal models have been extensively used to explain the mechanisms involved in this response, however, these models have limitations, since cellular response may vary between species [16].

Mathematical models have been applied to understand the dynamics of TB. At this respect, in [19], Kirschner and collaborators use a model to predict cell mediated response against TB. Marino and Kischner [11] extended the model a two-compartmental model, which captures the interaction of the immune cells and Mtb in the lungs and lymphs. In [9], the same authors explore the role of $CD8^+T$ cells. They describe the dynamics of cytokines, which are secreted as a result of antigen recognition by infected macrophages, as well as those secreted by activated macrophages, $CD4^+T$ and $CD8^+T$ cells. They use numerical simulations and sensitivity analysis to predict and explain possible disease outcomes due to the dynamics of the cytokines. On the other hand, Magombedze et al. [10] develop a model for human TB at the site of infection in the lungs. As in [9], the authors examine the effects of cytotoxic lymphocytes and other immune mechanisms to determine when an individual infected with TB will develop active or latent TB, but they do

not consider cytokines as dynamical variables. The model proposed consists of the interaction among two bacterial populations, three macrophage populations, helper T cells, and cytotoxic T cells.

We observe that in the works of Kirschner and Magombedze, the total bacteria population is divided in two classes: (a) intracellular bacteria which are found inside the macrophages, and (b) extracellular bacteria. Latency and active TB are characterized by the number of intracellular and extracellular bacteria, respectively.

In this work we formulate a mathematical model for the dynamics of Mtb. We consider the minimum number of variables describing the principal features of the cellular immunology against TB. The objective of our work is to obtain threshold conditions depending on the parameters that characterize infection progression. We give a global analysis of the dynamics of Mtb, macrophages and T cells.

The paper is organized in the following way. In the second section we formulate the mathematical model. In the third and fourth sections we do the qualitative analysis of the model. In fifth and sixth sections we present numerical results and discussion, respectively.

2. **The model.** Cell mediated response plays a fundamental role in the outcome of Mtb infection. A granuloma is formed at the site of the bacteria implantation, and its structure is mediated by a specific immune response induced by macrophages, T cells, and cytokines produced by them.

We formulate a mathematical model for cell mediated response against TB considering the population of uninfected macrophages, infected macrophages, Mtb bacteria, and T cells, denoted by $\bar{M}_U$, $\bar{M}_I$, B, and $\bar{T}$, respectively. 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.

We assume that uninfected macrophages reproduce at constant rate Λ_U, and die at a per capita constant rate μ_U. Uninfected macrophages become infected at a rate proportional to the product of $\bar{M}_U$ and B, with constant of proportionality β, and once infected die at per capita constant rate μ_I, where $\mu_I \geq \mu_U$. T cells eliminate infected macrophages at a rate proportional to the product $\bar{M}_I$ and $\bar{T}$, with constant of proportionality $\bar{\alpha}_T$.

Mtb bacteria multiply inside an infected macrophage up to a limit at which the macrophage bursts, and releases bacteria. For this reason, we assume that the growth rate of Mtb bacteria is $\bar{r}\mu_I\bar{M}_I$ where $\bar{r}$ is the average number of bacteria produced inside an infected macrophage. The releasing bacteria become temporarily extracellular, and they infect macrophages, or are ingested and killed by uninfected macrophages at a rate proportional to the product of $\bar{M}_U$ and B with constant of proportionality $\bar{\gamma}_U$. Mtb die at per capita rate μ_B.

In the presence of bacteria and infected macrophages, the supply of specific T-cells is given by

$$k_I\left(1-\bar{T}/T_{max}\right)\bar{M}_I,$$

where k_I is the growth rate of T cells, and T_{max} is the maximum T cell population level. Finally, the T-cells die at per capita rate μ_T.

The assumptions above lead to the following system of nonlinear differential equations

$$\begin{aligned}
\frac{d\bar{M}_U}{dt} &= \Lambda_U - \mu_U \bar{M}_U - \beta B \bar{M}_U \\
\frac{d\bar{M}_I}{dt} &= \beta B \bar{M}_U - \bar{\alpha}_T \bar{M}_I \bar{T} - \mu_I \bar{M}_I \\
\frac{dB}{dt} &= \bar{r}\mu_I \bar{M}_I - \bar{\gamma}_U \bar{M}_U B - \mu_B B \\
\frac{d\bar{T}}{dt} &= \left(1 - \frac{\bar{T}}{T_{max}}\right) \bar{k}_I \bar{M}_I - \mu_T \bar{T}.
\end{aligned} \tag{1}$$

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

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

In the new variables the system (1) becomes

$$\begin{aligned}
\frac{dM_U}{dt} &= \mu_U - \mu_U M_U - \beta B M_U \\
\frac{dM_I}{dt} &= \beta B M_U - \alpha_T M_I T - \mu_I M_I \\
\frac{dB}{dt} &= r M_I - \gamma_U M_U B - \mu_B B \\
\frac{dT}{dt} &= (1 - T)\, k_I M_I - \mu_T T,
\end{aligned} \tag{2}$$

where,

$$\alpha_T = \bar{\alpha}_T T_{max}, \gamma_U = \frac{\bar{\gamma_U}\Lambda_U}{\mu_U}, k_I = \frac{\bar{k}_I \Lambda_U}{T_{max}\mu_U}, r = \frac{\bar{r}\mu_I \Lambda_U}{\mu_U}.$$

The set of biological interest is given by

$$\Omega = \left\{(M_U, M_I, B, T) \in \mathbb{R}^4_+ : 0 \le M_U + M_I \le 1, B \le B_M, T \le T_M\right\}, \tag{3}$$

where $B_M = \dfrac{r}{\mu_B}$, and $T_M = \dfrac{k_I}{\mu_T + k_I}$.

The following lemma ensures that system (2) has biological sense, that is, all solutions starting in Ω remain there for all $t \ge 0$.

Lemma 2.1. *The set Ω defined in (3) is positively invariant for the solutions of the system (2).*

Proof. To see that $M_U + M_I \le 1$ we add the first two equations of (2), and using the fact that $\mu_I \ge \mu_U$ we obtain

$$\frac{d}{dt}(M_U + M_I) + \mu_U(M_U + M_I) \le \mu_U - \alpha_T M_I T \le \mu_U. \tag{4}$$

The solution of inequality (4) is given by $M_U + M_I \le 1 + (-1 + M_U^0 + M_I^0)e^{-\mu_U t}$, where the initial conditions satisfy $M_U^0 + M_I^0 \le 1$, therefore $M_U + M_I \le 1$ for all $t \ge 0$. Similarly, we prove that $B \le B_M$ and $T \le T_M$. On the other hand, it can be easily verified that the vector field defined by (2) points to the interior of Ω. Therefore the solutions starting in Ω remain there for all $t \ge 0$. □

3. **Equilibrium solutions.** In this section we will characterize the equilibrium solutions of the system (2). Before infection, the system is at the equilibrium $M_U = 1$, $M_I = 0$, $B = 0$, and $T = 0$. Suppose that bacteria enter to the organism. The infection progression will depend on a condition very similar to the one used in epidemiology for the spread of an infectious disease in a population of host individuals. The crucial quantity is the *basic reproductive number,* R_0, defined as

$$R_0 = \frac{r\beta}{\mu_I(\gamma_U + \mu_B)}. \tag{5}$$

The parameter R_0 can be interpreted biologically as follows: one infected cell gives rise to $r\beta/(\gamma_U + \mu_B)$ new infected cells per unit of time when the other cells are uninfected. Then, $\frac{1}{\mu_I}\left(\frac{r\beta}{\gamma_U + \mu_B}\right)$ is the number of secondary infections that arises from a macrophage during its lifetime if all other macrophages are uninfected.

The following theorem proves the existence results of the equilibria.

Theorem 3.1. *If $R_0 \leq 1$, then $E_1 = (1, 0, 0, 0)$ is the only equilibrium in Ω. If $R_0 > 1$, in addition to E_1, there exists an infected equilibrium, $E_2 = (M_U^*, M_I^*, B^*, T^*)$.*

Proof. Setting the system (2) equal to zero we obtain the following algebraic system

$$\begin{aligned} \mu_U - \mu_U M_U^* - \beta B^* M_U^* &= 0 \\ \beta B^* M_U^* - \alpha_T M_I^* T^* - \mu_I M_I^* &= 0 \\ r M_I^* - \gamma_U M_U^* B^* - \mu_B B^* &= 0 \\ (1 - T^*)\, k_I M_I^* - \mu_T T^* &= 0. \end{aligned} \tag{6}$$

A solution of (6) is the infection-free equilibrium $E_1 = (1, 0, 0, 0)$. Now we are going to determine the existence of nontrivial equilibria. From the fourth equation of (6) we have

$$M_I^* = \frac{\mu_T T^*}{(1 - T^*)k_I}. \tag{7}$$

Since $T^* \leq T_M$, then

$$\frac{\mu_T T^*}{(1 - T^*)k_I} \leq \frac{\mu_T T_M}{(1 - T_M)k_I} = 1,$$

which implies $0 \leq M_I^* \leq 1$. On the other hand, from first equation of (6) we have

$$B^* = \frac{\mu_U(1 - M_U^*)}{\beta M_U^*}. \tag{8}$$

From the second and third equation of (6), we obtain the following relations

$$\frac{B^*}{M_I^*} = \frac{\alpha_T T^* + \mu_I}{\beta M_U^*} \tag{9}$$

$$\frac{B^*}{M_I^*} = \frac{r}{\gamma_U M_U^* + \mu_B}. \tag{10}$$

Setting equal equations (9) and (10), we obtain

$$\frac{\alpha_T T^* + \mu_I}{\beta M_U^*} = \frac{r}{\gamma_U M_U^* + \mu_B}, \tag{11}$$

in consequence

$$M_U^* = \frac{\mu_B(\alpha_T T^* + \mu_I)}{r\beta - \gamma_U(\alpha_T T^* + \mu_I)}. \tag{12}$$

In order to have a feasible endemic equilibrium, the condition $0 < M_U^* < 1$ must hold. It is clear that $M_U^* > 0$ if and only if $r\beta - \gamma_U(\alpha_T T^* + \mu_I) > 0$. It can be seen that last inequality implies

$$T^* < T_M^*, \tag{13}$$

where

$$T_M^* = \frac{\mu_I\mu_B R_0 + \mu_I\gamma_U(R_0 - 1)}{\gamma_U\alpha_T}. \tag{14}$$

On the other hand, $M_U^* \leq 1$ if and only if $T^* \leq \frac{\alpha_T}{\mu_I}(R_0 - 1)$. Therefore, there is at least one solution $T^* > 0$ if and only if $R_0 > 1$. We are going to use the equations (7)-(12) to determine the uniqueness of T^*. Substituting the equations (7) and (8) in (11) we have

$$\mu_U(1 - M_U^*) = \frac{\mu_T T^*}{(1 - T^*)k_I}(\alpha_T T^* + \mu_I). \tag{15}$$

Substituting M_U^* defined by (12) in (15), we obtain

$$\begin{aligned}[r\beta - \gamma_U(\alpha_T T^* + \mu_I)]\,[\mu_U k_I(1 - T^*) - \mu_T T^*(\alpha_T T^* + \mu_I)] \\ -\mu_B\mu_U k_I(1 - T^*)(\alpha_T T^* + \mu_I) = 0.\end{aligned} \tag{16}$$

From equation (16) we conclude that T^* is a zero of the function f defined by

$$\begin{aligned}f(T) = &-\mu_T\alpha_T\,[r\beta - \gamma_U(\alpha_T T + \mu_I)]\left[T^2 + \frac{\mu_U k_I + \mu_T\mu_I}{\mu_T\alpha_T}T - \frac{\mu_U k_I}{\mu_T\alpha_T}\right] \\ &-\mu_B\mu_U k_I(1 - T)(\alpha_T T + \mu_I).\end{aligned} \tag{17}$$

Observe that

$$T^2 + \frac{\mu_U k_I + \mu_T\mu_I}{\mu_T\alpha_T}T - \frac{\mu_U k_I}{\mu_T\alpha_T} = (T - \zeta)(T - \eta), \tag{18}$$

where

$$\begin{aligned}\zeta &= \frac{-\frac{\mu_U k_I + \mu_T\mu_I}{\mu_T\alpha_T} + \sqrt{\left(\frac{\mu_U k_I + \mu_T\mu_I}{\mu_T\alpha_T}\right)^2 + 4\frac{\mu_U k_I}{\mu_T\alpha_T}}}{2}, \\ \eta &= \frac{-\frac{\mu_U k_I + \mu_T\mu_I}{\mu_T\alpha_T} - \sqrt{\left(\frac{\mu_U k_I + \mu_T\mu_I}{\mu_T\alpha_T}\right)^2 + 4\frac{\mu_U k_I}{\mu_T\alpha_T}}}{2}.\end{aligned}$$

It is clear that $\eta < 0$. Furthermore, from inequality $\mu_I \geq \mu_U$ we have $\zeta \leq T_M$. Now, replacing (18) in (17) we can rewrite f by

$$\begin{aligned}&f(T) \\ &= -\mu_T\alpha_T\,[r\beta - \gamma_U(\alpha_T T + \mu_I)]\,(T - \zeta)(T - \eta) - \mu_B\mu_U k_I(1 - T)(\alpha_T T + \mu_I).\end{aligned}$$

Observe that $f(\zeta) = -\mu_B\mu_U k_I(1-\zeta)(\alpha_T\zeta+\mu_I) < 0$. On the other hand, expanding f we obtain

$$f(T) = b_3T^3 + b_2T^2 + b_1T + b_0,$$

where

$$\begin{aligned}b_3 &= \mu_T\gamma_U\alpha_T^2 \\ b_2 &= \mu_U k_I\alpha_T(\gamma_U + \mu_B) - \mu_T\mu_I[r\beta - \gamma_U(\mu_I + \alpha_T)] \\ b_1 &= -[\mu_U k_I\alpha_T(\gamma_U + \mu_B) + \mu_T\mu_I(r\beta - \mu_I\gamma_U) + \mu_B k_I\mu_I(\gamma_U + \mu_B)(R_0 - 1)] \\ b_0 &= \mu_B k_I\mu_I(\gamma_U + \mu_B)(R_0 - 1).\end{aligned}$$

Since $f(\zeta) < 0$, and $f(0) = b_0 > 0$ for $R_0 > 1$ there exists at least one root T^* of f in the interval $(0, \zeta)$. To determine the location of the other roots, we will use Descartes' Rule of Signs. Note that b_0 and b_3 are positive, b_1 is always negative, while b_2 can be positive or negative. The change of coefficient signs can be determined from the following table

b_3	b_2	b_1	b_0
+	+	-	+
+	-	-	+

Since there are two changes of sign in both cases, the Descartes rule implies the existence of only one negative root and zero or two positive roots. We already know the existence of one positive root $T^* < T_M$, therefore $f(T)$ has one negative root and two positive roots. Since the roots of $f(T)$ have to be less than T_M, and T_M^*, then they have to be less than $\widetilde{T} = \min\{T_M, T_M^*\}$. In order to prove that $f(T)$ has only one root between zero and $\widetilde{T}$, it is enough to prove that $f(\tilde{T}) < 0$. If $\widetilde{T} = T_M$, then $T_M < T_M^*$, and therefore

$$r\beta - \gamma_U(\alpha_T T_M + \mu_I) > r\beta - \gamma_U(\alpha_T T_M^* + \mu_I) = 0,$$

that implies

$$\begin{aligned} f(\widetilde{T}) = f(T_M) &= -\mu_T\alpha_T\left[r\beta - \gamma_U(\alpha_T T_M + \mu_I)\right](T_M - \zeta)(T_M - \eta) \\ &\quad -\mu_B\mu_U k_I(1 - T_M)(\alpha_T T_M + \mu_I) < 0. \end{aligned}$$

If $\widetilde{T} = T_M^*$ then $T_M^* < T_M < 1$, therefore

$$f(\widetilde{T}) = f(T_M^*) = -\mu_B\mu_U k_I(1 - T_M^*)(\alpha_T T_M^* + \mu_I) < 0,$$

that is, $f(\widetilde{T}) < 0$. Since $f(0) > 0$, there is a unique root of $f(T) = 0$ in $[0, \widetilde{T}]$. □

4. **Stability of equilibrium solutions.** In this section we analyze the stability of equilibria. We begin by analyzing the stability of the infection-free equilibrium.

Theorem 4.1. *For $R_0 < 1$, E_1 is locally asymptotically stable, and for $R_0 > 1$, E_1 is unstable.*

Proof. The Jacobian of system (1) evaluated at E_1 is

$$J(E_1) = \begin{pmatrix} -\mu_U & 0 & -\beta & 0 \\ 0 & -\mu_I & \beta & 0 \\ 0 & r & -(\gamma_U + \mu_B) & 0 \\ 0 & k_I & 0 & -\mu_T \end{pmatrix}.$$

The characteristic polynomial of $J(E_1)$ is

$$p(\lambda) = (\lambda + \mu_U)(\lambda + \mu_T)\left[\lambda^2 + (\mu_I + \gamma_U + \mu_B)\lambda + \mu_I(\gamma_U + \mu_B) - r\beta\right].$$

In consequence, the eigenvalues of $J(E_1)$ are $\lambda_1 = -\mu_U$, $\lambda_2 = -\mu_T$ and the roots of the quadratic equation

$$\lambda^2 + (\gamma_U + \mu_B + \mu_I)\lambda - \mu_I(\gamma_S + \mu_B)(R_0 - 1) = 0. \tag{19}$$

From Routh-Hurwitz criteria we conclude that the roots of the equation (19) have negative real part if and only if $R_0 < 1$. Therefore, for $R_0 < 1$, E_1 is locally asymptotically stable and, for $R_0 > 1$, E_1 is unstable. □

Actually, we can prove global stability of E_1 when $R_0 \leq 1$.

Theorem 4.2. *If $R_0 \leq 1$ then E_1 is globally asymptotically stable.*

Proof. The function V defined by

$$V = rM_I + \mu_I B, \tag{20}$$

satisfies $V(E_1) = 0$ and $V(x) \geq 0$ for all $x \in \Omega$. Since $R_0 \leq 1$ implies $r\beta - \mu_I\gamma_U \leq \mu_I\mu_B$, then its orbital derivative satisfies

$$\begin{aligned} \dot{V} &= BM_U(r\beta - \mu_I\gamma_U) - (r\alpha_T M_I T + \mu_B\mu_I B) \\ &\leq \mu_I\mu_B B(M_U - 1) - r\alpha_T M_I T \\ &\leq 0. \end{aligned}$$

In consequence $\dot{V}(x) \leq 0$ for all $x \in \Omega$. From inspection of system (2) we can see that the maximum invariant set contained in the set $\dot{V} = 0$ is the plane $B = 0$, $M_I = 0$. In this set, system (2) becomes

$$\frac{dM_U}{dt} = \mu_U - \mu_U M_U, \quad \frac{dM_I}{dt} = 0, \quad \frac{dB}{dt} = 0, \quad \frac{dT}{dt} = -\mu_T T.$$

Which implies that the solutions starting there tend to equilibrium E_1 as t goes to infinity. Therefore, applying the LaSalle-Lyapunov Theorem (see [8]) we have that E_1 is globally asymptotically stable. □

In the following we will prove that $\Omega - \{(M_U, 0, 0, T) \,|\, 0 \leq M_U \leq 1, 0 \leq T \leq T_M\}$ is an asymptotic stability region for the endemic equilibrium E_2 when $R_0 > 1$ and $\gamma_U \leq \mu_B$. For this, we use the following Lyapunov function

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

where a_1 is a positive constant and

$$\begin{aligned} a_2 &= \left(\frac{\mu_U}{\beta B^* M_U^*}\frac{\mu_B}{\gamma_U} - 1\right)a_1, \quad a_3 = \frac{\mu_U}{\beta B^* M_U^*}\frac{\mu_B}{\gamma_U}\,a_1 \quad a_4 = \frac{\mu_U M_U^*}{\beta B^* M_U^*}\,a_1 \\ a_5 &= \frac{\mu_U M_U^*}{\gamma_U M_U^* B^*}\,a_1 \quad a_6 = \frac{\alpha_T T^* M_I^*}{k_I M_I^*(1 - T^*)}\frac{\mu_U M_U^*}{\beta B^* M_U^*}\left(\frac{\mu_B}{\gamma_U M_U^*} + 1\right)a_1. \end{aligned} \tag{21}$$

To prove the global stability of E_2 using Lyapunov direct method we have to show that $V(x) \geq 0$ and $\dot{V}(x) < 0$ for all $x \in \operatorname{int}\Omega$. For this end we need the results given in next theorems.

Theorem 4.3. *The orbital derivative $\dot{V}$ of V is equal to $\dot{V} = -f$ where f is given by*

$$
\begin{aligned}
&f(x,y,z,w)\\
=&(a_1+a_2)\left[\mu_U M_U^*\left(x+\frac{1}{x}-2\right)+\beta B^* M_U^*\left(xz+\frac{1}{x}-z-1\right)\right]\\
&+(a_3+a_4)\left[\beta B^* M_U^*\left(\frac{xz}{y}+y-xz-1\right)+\alpha_T T^* M_I^*(yw+1-y-w)\right]\\
&+a_5 r M_I^*\left(\frac{y}{z}+z-y-1\right)+a_5\gamma_U M_U^* B^*(xz+1-x-z)\\
&+a_6 k_I M_I^*\left(\frac{y}{w}+w-y-1\right)+a_6 k_I M_I^* T^*(wy+1-w-y), \qquad (22)
\end{aligned}
$$

and $x = M_U/M_U^*$, $y = M_I/M_I^*$, $z = B/B^*$ *and* $w = T/T^*$.

Proof. The orbital derivative of V is given by

$$
\begin{aligned}
\dot{V}(X) &= (a_1+a_2)\left(1-\frac{M_U^*}{M_U}\right)(\mu_U-\mu_U M_U-\beta B M_U)\\
&\quad+(a_3+a_4)\left(1-\frac{M_I^*}{M_I}\right)(\beta B M_U-\alpha_T T M_I-\mu_I M_I)\\
&\quad+a_5\left(1-\frac{B^*}{B}\right)(rM_I-\gamma_U M_U B-\mu_B B)\\
&\quad+a_6\left(1-\frac{T^*}{T}\right)[k_I(1-T)M_I-\mu_T T]. \qquad (23)
\end{aligned}
$$

From the equilibrium equations (6) we have

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

Replacing μ_U, μ_I, μ_B and μ_T in (23) we obtain

$$
\begin{aligned}
&\dot{V}\\
=&-(a_1+a_2)\left[\mu_U M_U^*\left(\frac{M_U}{M_U^*}+\frac{M_U^*}{M_U}-2\right)+\beta B^* M_U^*\left(\frac{BM_U}{B^*M_U^*}+\frac{M_U^*}{M_U}-\frac{B}{B^*}-1\right)\right]\\
&-(a_3+a_4)\beta B^* M_U^*\left(\frac{BM_U M_I^*}{B^*M_U^*M_I}+\frac{M_I}{M_I^*}-\frac{BM_U}{B^*M_U^*}-1\right)\\
&+(a_3+a_4)\alpha_T T^* M_I^*\left(\frac{TM_I}{T^*M_I^*}+1-\frac{M_I}{M_I^*}-\frac{T}{T^*}\right)\\
&-a_5 r M_I^*\left(\frac{B^*M_I}{BM_I^*}+\frac{B}{B^*}-\frac{M_I}{M_I^*}-1\right)-a_5\gamma_U M_U^* B^*\left(\frac{M_U B}{M_U^*B^*}+1-\frac{B}{B^*}-\frac{M_U}{M_U^*}\right)\\
&-a_6 k_I M_I^*\left(\frac{T^*M_I}{TM_I^*}+\frac{T}{T^*}-\frac{M_I}{M_I^*}-1\right)-a_6 k_I M_I^* T^*\left(\frac{TM_I}{T^*M_I^*}+1-\frac{T}{T^*}-\frac{M_I}{M_I^*}\right). \qquad (24)
\end{aligned}
$$

In the variables

$$
x=\frac{M_U}{M_U^*},\ y=\frac{M_I}{M_I^*},\ z=\frac{B}{B^*},\ w=\frac{T}{T^*},
$$

we have $\dot{V}(x,y,z,w) = -f(x,y,z,w)$. □

Theorem 4.4. *If $\gamma_U \leq \mu_B$ then the function f is nonnegative.*

Proof. From the following equalities

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

we obtain the constants defined in (21). It is clear that $a_3,\ldots,a_6$ are positive, and since $\gamma_U \leq \mu_B$ then $a_2 > 0$. Replacing the equilibrium equation $rM_I^* = \gamma_U M_U^* B^* + \mu_B B^*$ and the constants (21) in the function f we have

$$\begin{aligned}f(x,y,z,w) &= a_2\mu_U M_U^*\left(x+\frac{1}{x}-2\right)+(a_3+a_4)\beta B^* M_U^*\left(\frac{xz}{y}+\frac{y}{z}+\frac{1}{x}-3\right) \\ &\quad +a_6 k_I M_I^* y\left(\frac{1}{w}+w-2\right),\end{aligned} \tag{25}$$

Taking $d_1 = x$, $d_2 = y$, $d_3 = z$ and $d_4 = w$ in the inequality $\sum_{i=1}^n d_i \geq n\sqrt{\prod_{i=1}^n d_i}$, it can be seen readily that the expressions inside the parenthesis of (25) are nonnegative, and therefore f is nonnegative. □

Theorem 4.5. *If $\gamma_U \leq \mu_B$ then nontrivial equilibrium E_2 is globally asymptotically stable.*

Proof. It is clear that $V(E_2) = 0$ and $V(x) \geq 0$ for all $x \in \operatorname{int}\Omega$. From Theorem 4.3 we have $\dot{V} = -f$ and from Theorem 4.4 we have f is nonnegative, therefore $\dot{V}(x) \leq 0$ for all $x \in \operatorname{int}\Omega$. Further $\dot{V} = 0$ if and only if $M_U = M_U^*$, $M_I = M_I^*$, $B = B^*$ and $T = T^*$ which implies all trajectories inside Ω approach E_2 when t goes to infinity. Finally, it can be easily verified that the vector field defined by (2) over the set

$$\partial\Omega - \{(M_U,0,0,T) \in \Omega_1 : 0 \leq M_U \leq 1,\ 0 \leq T \leq T_M\},$$

points to the interior of Ω. □

5. **Numerical solutions.** In this section we present numerical simulations and graphs illustrating the population growth of Mtb bacteria, T cells, infected and uninfected macrophages. The values of the parameters used in the simulations are given in Table 1.

Recall that R_0 is the number of secondary infections that arises from one infected macrophage when all the other are uninfected. In terms of the original parameters, R_0 is equal to

$$R_0 = \frac{\bar{r}\frac{\Lambda_U}{\mu_U}\beta}{\bar{\gamma}_U\frac{\Lambda_U}{\mu_U}+\mu_B}, \tag{26}$$

where $\bar{r}$ is the average number of bacteria produced inside an infected macrophage; β is the infection rate; μ_B is the natural death rate of bacteria; $\bar{\gamma}_U$ is the death rate of bacteria due to uninfected macrophages; and finally, Λ_U, and μ_U are the birth and death rates of uninfected macrophages, respectively.

Parameters	Figure 1	Figure 2	Figure 3	Units
α_T	0.1	0.1	0.1	day^{-1}
$\bar{\alpha}_T$	$2 * 10^{-5}$	$2 * 10^{-5}$	$2 * 10^{-5}$	$\text{T}^{-1}\text{day}^{-1}$
β	$8.25 * 10^{-9}$	$8.25 * 10^{-8}$	$8.25 * 10^{-7}$	$\text{B}^{-1}\text{day}^{-1}$
γ_U	0.0879	0.0879	0.0879	$\text{MB}^{-1}\text{day}^{-1}$
$\bar{\gamma}_U$	$2.9 * 10^{-7}$	$2.9 * 10^{-7}$	$2.9 * 10^{-7}$	$\text{B}^{-1}\text{day}^{-1}$
μ_B	0.012	0.012	0.012	day^{-1}
μ_I	0.011	0.011	0.011	day^{-1}
μ_T	0.33	0.33	0.33	day^{-1}
μ_U	0.0033	0.0033	0.0033	day^{-1}
k_I	0.484848	0.484848	0.484848	day^{-1}
$\bar{k}_I$	0.008	0.008	0.008	$\text{TM}^{-1}\text{day}^{-1}$
r	5*0.011	5*0.011	5*0.011	day^{-1}
T_{max}	50000	50000	50000	T
Λ_U	1000	1000	1000	M day^{-1}

TABLE 1. Parameter values were estimated using data given in [9, 1].

We see that the outcome of Mtb infection depends mainly on the interplay of the parameters β, $\bar{r}$ and $\bar{\gamma}_U$ since the other parameters (Λ_U, μ_U, and μ_B) are unaffected by the stage of the disease. We present numerical simulations with different values of β, keeping fixed the others parameters (see Table 1) to see how this parameter influences the differences in outcome.The same can be done for γ_U and $\bar{r}$. In Figure 1, $\beta = 8.25 * 10^{-9}$ with $R_0 = 0.125$. In this case the initial population of bacteria and infected macrophages decreases to zero. In Figure 2, the value of β increases to $8.25 * 10^{-8}$, and $R_0 = 1.25$, indicating Mtb infection. We notice a peak in the populations of infected macrophages, T cells, and bacteria in the early stage of the infection, which is consistent with the results reported by Egen J.G. *et al.* [6]. These authors found that during the granuloma formation, TNF-α cytokines send signals promoting the interaction between macrophages and T cells. We observe that this cell activity allows efficient control of the bacteria replication, and the time of the immune response could coincide with the average time of the granuloma formation [15]. The same figure shows that in the steady state the number of uninfected macrophages is much bigger than the number of infected macrophages, and bacteria which may be interpreted as a latency steady state, where the bacteria is controlled by the immune system.

Figure 3 illustrates the behavior of bacteria and cell populations for $\beta = 8.25 * 10^{-7}$. In this case, $R_0 = 12.5$, indicating that on average there are around 12 new infected macrophages per day per infected macrophages at the beginning of the infection which shows a significant proliferation of infected cells [9]. We observe that macrophages and T cells populations are much smaller than bacteria population. This could indicate an active infection situation where, in spite of the increment of macrophages and T cells, bacteria are able to evade the immune response of the host.

6. **Discussion.** In this paper we formulated a mathematical model on the immune response to Mtb in order to evaluate the effectiveness of macrophages and T cells in controlling TB.

Although our model is quite simple compared to the complexity of the immune response to Mtb, it predicts in terms of the basic reproductive number R_0, when the bacteria is cleared or infection progresses to disease. R_0 represents the number of infected macrophages resulting from one infected macrophage if all other macrophages are uninfected. It is directly proportional to Mtb growth at its equilibrium level, $\bar{r}\frac{\Lambda_U}{\mu_U}$, and infection rate, β, and it is inversely proportional to death related to the immune system plus natural death rate of bacteria, $\bar{\gamma}_U\frac{\Lambda_U}{\mu_U}+\mu_B$. If $R_0 \leq 1$, bacteria and infected macrophages will decrease and ultimately will be eliminated. This scenario occurs when Mtb is not able to infect macrophages in sufficient numbers, or the growth of bacteria is very low, or the immune response is able to control infection. When $R_0 > 1$, there is an endemically infected steady state, E_2, where bacteria and infected macrophages are present. This steady state could represent latent or active TB, depending on the amount of bacteria.

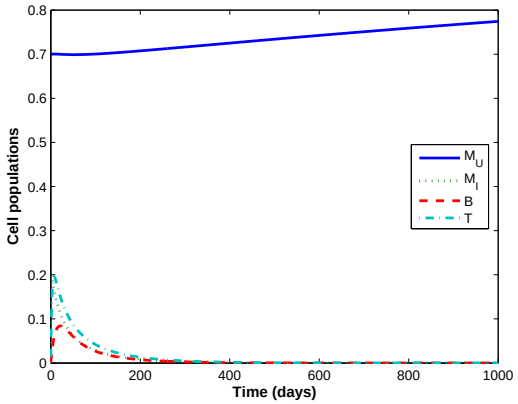

FIGURE 1. Temporal course of M_U, M_I, B and T using the parameter values given in Table 1 for Figure 1. In this case $R_0 = 0.125$, and Mtb is eliminated.

The temporal behavior of the cellular response is reflected in Figures 2 and 3. At the beginning of infection was observed proliferation of bacteria and immune cells, followed by a decrease in both populations, which are approaching a steady state over time.

As mentioned in the introduction, it is reasonable to assume that the bacterial load can be used as a marker of disease progression. According to this, Figure 2 may reflect a state of latency where the bacteria is controlled by the immune system, while Figure 3 could describe active TB.

Using a murine model, Sköld et al [14] demonstrated that circulating monocytes also have the ability to give rise to dendritic cells, macrophages as well as to control the bacterial population. Several authors [20, 2] have proposed that dendritic cells phagocytize Mtb and activate T cells more efficiently than macrophages. According to these reports, dendritic cells and neutrophils may be important in controlling the bacteria. Mathematical models that include the role of these cells in the immune response should be considered in the future.

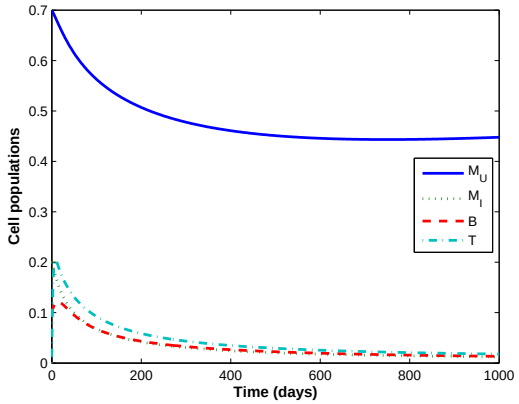

FIGURE 2. Temporal course of M_U, M_I, B and T using the parameter values given in Table 1 for Figure 2. In this case $R_0 = 1.25$, and Mtb progression is controlled.

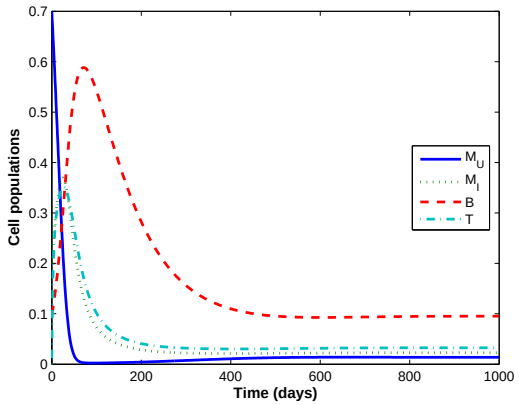

FIGURE 3. Temporal course of M_U, M_I, B and T using the parameter values given in Table 1 for Figure 3. In this case $R_0 = 12.5$, and Mtb is not controlled.

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