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A MATHEMATICAL MODEL WITH OPTIMAL CONTROLS FOR CELLULAR IMMUNOLOGY OF TUBERCULOSIS

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Abstract. In this paper 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 infection-free equilibrium and the endemically infected equilibrium. And we analyze the dynamics of this model, characterize the optimal controls related to drug therapy, and discuss a quadratic control and a linear control. The quadratic control allows for a weaker treatment that more effectively than the linear control.

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 [1, 2]. However, only 10% of infected individuals with Mtb develop the disease in their lifetime [3]. 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 populations, such as $CD4^+T$ or $CD8^+T$ lymphocytes. These cells secrete cytokines that help to kill the infected macrophages [4].

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

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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 [5]. 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 [6].

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 [7].

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. It worth to mention that in any case the bacteria will primarily be inside the granulomas [6].

It is believed that granulomas are advantageous to the host since they contain and restrict mycobacteria [5]. 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 [8].

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 [9].

Mathematical models have been applied to understand the dynamics of TB. At this respect, in [10], 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 [12], 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. [13] develop a model for human TB at the site of infection in the lungs. As in [12], 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 [12, 13], 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 firstly 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 with chemotherapy.

On the other hand, recent studies have illustrated the effective use of the Generalized Legendre Clebsch condition in a general class of mathematical models of cancer chemotherapy [14]. In [14], three control strategies are analyzed. One is a killing agent which is active during cell division, another is a blocking agent which slows down cell growth, and a third is the recruitment of dormant tumor cells to enhance their efficient treatment by a cytotoxic drug. Within this study, the authors have found the singular controls are not optimal. In [15], the authors have introduced a model that involves a cytotoxic chemotherapeutic control that can directly or indirectly kill tumor cells and have found regions in which the singular controls may be optimal. Ledzewicz et al. [16] provides insight into the use of quadratic and linear controls for a bilinear optimal control problem related to cancer chemotherapy. The form of the equations in [16] make the analytic computation of the Generalized Legendre Clebsch condition tractable. Within our work, we make use of the aforementioned strategy to study optimal control problems of the interaction with the immune and Mtb cells with chemotherapy.

2. Model Formulation

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, T cells, and chemotherapy drug concentration, denoted by $\bar{M}_U$, $\bar{M}_I$, B, $\bar{T}$, and C, 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 as in [6].

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 then 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 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

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

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 chemotherapy concentration *C* has an outside source term, $C_M(t)$, which represents treatment, and decays out of the system proportionally to the concentration through the term $-\eta C$. Chemotherapy affects all four cell populations through a mass-action dynamic of the form $K_1\bar{M}_U$, $K_2\bar{M}_I$, K_3B, $K_4\bar{T}$, with the differential effect of the medication on each cell type achieved through different values of the K_i(i=1, 2, 3, 4) parameters.

Here, we will consider two cases: (a)the input rate of chemotherapy drug is constant, C_M, (b)the input rate of chemotherapy drug is changeable, $C_M(t)$.

According to the assumptions above, we construct the following two systems

$$(1)\qquad \begin{cases} \dfrac{d\bar{M}_U}{dt} = \Lambda_U - \mu_U\bar{M}_U - \beta B\bar{M}_U - K_1C\bar{M}_U, \\ \dfrac{d\bar{M}_I}{dt} = \beta B\bar{M}_U - \bar{\alpha}_T\bar{M}_I\bar{T} - \mu_I\bar{M}_I - K_2C\bar{M}_I, \\ \dfrac{dB}{dt} = \bar{r}\mu_I\bar{M}_I - \bar{\gamma}_U\bar{M}_UB - \mu_BB - K_3CB, \\ \dfrac{d\bar{T}}{dt} = (1-\dfrac{\bar{T}}{T_{\max}})\bar{k}_I\bar{M}_I - \mu_T\bar{T} - K_4C\bar{T}, \\ \dfrac{dC}{dt} = -\eta C + C_M, \end{cases}$$

and

$$
(2)\qquad \begin{cases} \dfrac{d\bar{M}_U}{dt} = \Lambda_U - \mu_U \bar{M}_U - \beta B \bar{M}_U - K_1 C \bar{M}_U, \\ \dfrac{d\bar{M}_I}{dt} = \beta B \bar{M}_U - \bar{\alpha}_T \bar{M}_I \bar{T} - \mu_I \bar{M}_I - K_2 C \bar{M}_I, \\ \dfrac{dB}{dt} = \bar{r}\mu_I \bar{M}_I - \bar{\gamma}_U \bar{M}_U B - \mu_B B - K_3 C B, \\ \dfrac{d\bar{T}}{dt} = (1 - \dfrac{\bar{T}}{T_{\max}})\bar{k}_I \bar{M}_I - \mu_T \bar{T} - K_4 C \bar{T}, \\ \dfrac{dC}{dt} = -\eta C + C_M(t). \end{cases}
$$

In next section, we will analyze system (1). And system (2) with different control strategies will be considered in Section 4.

3. Existence and Stability of Equilibria of System (1)

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

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

Then system (1) is equivalent to

$$
(3)\qquad \begin{cases} \dfrac{dM_U}{dt} = \mu_U - \mu_U M_U - \beta B M_U - K_1 C M_U, \\ \dfrac{dM_I}{dt} = \beta B M_U - \alpha_T M_I T - \mu_I M_I - K_2 C M_I, \\ \dfrac{dB}{dt} = r M_I - \gamma_U M_U B - \mu_B B - K_3 C B, \\ \dfrac{dT}{dt} = (1 - T) k_I M_I - \mu_T T - K_4 C T, \\ \dfrac{dC}{dt} = -\eta C + C_M, \end{cases}
$$

where,

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

Obviously, the set of biological interest is given by

$$
(4)\quad \Omega = \{(M_U, M_I, B, T, C) \in \mathbb{R}^5_+ : M_U + M_I \le 1, B \le B_{\max}, T \le T_{\max}, C \le C_{\max}\},
$$

where $B_{\max} = \frac{r}{\mu_B}$, $T_{\max} = \frac{k_I}{\mu_T + k_I}$, and $C_{\max} = \frac{C_M}{\eta}$. The following lemma ensures that system (3) has biological sense, that is, all solutions starting in Ω remain there for all $t \ge 0$.

Lemma 3.1. *The set Ω defined in (4) is positively invariant for the solutions of the system (3).*

Proof. Add the first two equations of system (3), and using the fact that $\mu_I \geq \mu_U$, we obtain

$$\frac{d}{dt}(M_U + M_I) + \mu_U(M_U + M_I) \leq \mu_U - CK_1M_U - CK_2M_I - \alpha_T M_I T \leq \mu_U. \tag{5}$$

The solution of inequality (5) is given by $M_U + M_I \leq 1 + (-1 + M_U^0 + M_I^0)e^{-\mu_U t}$, where the initial conditions satisfy $M_U^0 + M_I^0 \leq 1$, therefore $M_U + M_I \leq 1$ for all $t \geq 0$. Similarly, we prove that $B \leq B_{\max}$, $T \leq T_{\max}$, and $C \leq C_{\max}$. Therefore the solutions starting in Ω remain there for all $t \geq 0$. ∎

In the rest of this section, we will consider the existence and stability of the equilibria of system (3) within region Ω. Before infection, the system is at the equilibrium $M_U = 1$, $M_I = 0$, $B = 0$, $T = 0$, and $C = C_{\max}$. 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

$$R_0 = \frac{r\beta}{(\mu_I + K_2C_{\max})(\gamma_U + \mu_B + K_3C_{\max})}. \tag{6}$$

The threshold R_0 can be interpreted biologically as follows: one infected cell gives rise to $r\beta/(\gamma_U + \mu_B + K_3C_{\max})$ new infected cells per unit of time when the other cells are uninfected. Then, $\frac{1}{\mu_I + K_2C_{\max}}(\frac{r\beta}{\gamma_U + \mu_B + K_3C_{\max}})$ is the number of secondary infections that arises from a macrophage during its lifetime if all other macrophages are uninfected.

We get the following theorems as our main results of this section.

Theorem 3.2. *If $R_0 \leq 1$, then $E_1 = (1, 0, 0, 0, C_{\max})$ is the only equilibrium in Ω. If $R_0 > 1$, in addition to E_1, there exists an infected equilibrium, $E_2 = (M_U^*, M_I^*, B^*, T^*, C^*)$.*

Proof. Let the right of system (3) equal to zero, then we obtain the following algebraic equations

$$\begin{cases} \mu_U - \mu_U M_U^* - \beta B^* M_U^* - K_1 C^* M_U^* = 0, \\ \beta B^* M_U^* - \alpha_T M_I^* T^* - \mu_I M_I^* - K_2 C^* M_I^* = 0, \\ rM_I^* - \gamma_U M_U^* B^* - \mu_B B^* - K_3 C^* B^* = 0, \\ (1 - T^*)k_I M_I^* - \mu_T T^* - K_4 C^* T^* = 0, \\ -\eta C^* + C_M = 0. \end{cases} \tag{7}$$

It is easy to see that a trivial solution of (7) is the infection-free equilibrium $E_1 = (1, 0, 0, 0, C_{\max})$. Now we are going to determine the existence of nontrivial equilibrium.

From the fifth equation of (7), we get $C^* = C_{\max}$.

From the fourth equation of (7), we get

$$M_I^* = \frac{(\mu_T + K_4 C^*)T^*}{(1 - T^*)k_I}. \tag{8}$$

Since $T^* \leq T_M$, then

$$\frac{(\mu_T + K_4 C^*)T^*}{(1 - T^*)k_I} \leq \frac{(\mu_T + K_4 C^*)T_M}{(1 - T_M)k_I} = 1,$$

which implies $0 \leq M_I^* \leq 1$.

From the first equation of (7), we have

$$B^* = \frac{\mu_U(1 - M_U^*) - K_1 C^* M_U^*}{\beta M_U^*}. \tag{9}$$

From the second and third equations of (7), we obtain the following relations

$$\frac{B^*}{M_I^*} = \frac{\alpha_T T^* + \mu_I + K_2 C^*}{\beta M_U^*}, \tag{10}$$

$$\frac{B^*}{M_I^*} = \frac{r}{\gamma_U M_U^* + \mu_B + K_3 C^*}. \tag{11}$$

By equations (10) and (11), we obtain

$$\frac{\alpha_T T^* + \mu_I + K_2 C^*}{\beta M_U^*} = \frac{r}{\gamma_U M_U^* + \mu_B + K_3 C^*}, \tag{12}$$

and from which we get

$$M_U^* = \frac{(\mu_B + K_3 C^*)(\alpha_T T^* + \mu_I + K_2 C^*)}{r\beta - \gamma_U(\alpha_T T^* + \mu_I + K_2 C^*)}. \tag{13}$$

In order to search for a feasible endemic equilibrium, the condition $0 < M_U^* < 1$ must hold. It is clear that $M_U^* > 0$ if and only if $r\beta - \gamma_U(\alpha_T T^* + \mu_I + K_2 C^*) > 0$. It can be seen that the last inequality implies

$$T^* < T_M^*, \tag{14}$$

where

$$T_M^* = \frac{(\mu_I + K_2 C^*)(\mu_B + K_3 C^*)R_0 + (\mu_I + K_2 C^*)\gamma_U(R_0 - 1)}{\gamma_U \alpha_T}. \tag{15}$$

On the other hand, $M_U^* \leq 1$ if and only if $T^* \leq \frac{(\mu_I+K_2C^*)(R_0-1)}{\alpha_T}$. Therefore, there is at least one solution $T^* > 0$ if and only if $R_0 > 1$. We are going to use the equations (8)-(13) to determine the uniqueness of T^*. Substituting the equations (8) and (9) into (10), we have

$$\mu_U(1-M_U^*) - K_1C^*M_U^* = \frac{(\mu_T + K_4C^*)T^*}{(1-T^*)k_I}(\alpha_T T^* + \mu_I + K_2C^*). \tag{16}$$

Substituting M_U^* defined by (13) into (16), we obtain

$$\begin{aligned} &[r\beta - \gamma_U(\alpha_T T^* + \mu_I + K_2C^*)][\mu_U k_I(1-T^*) \\ &-T^*(\mu_T + K_4C^*)(\alpha_T T^* + \mu_I + K_2C^*)] \\ &-\mu_U k_I(\mu_B + K_3C^*)(K_1C^*+1)(1-T^*)(\alpha_T T^* + \mu_I + K_2C^*) = 0. \end{aligned} \tag{17}$$

From equation (17), we conclude that T^* is a zero of the function f defined by

$$\begin{aligned} f(T) = &-\alpha_T(\mu_T + K_4C^*)[r\beta - \gamma_U(\alpha_T T + \mu_I + K_2C^*)]\times \\ &[T^2 + \frac{\mu_U k_I + (\mu_T + K_4C^*)(\mu_I + K_2C^*)}{\alpha_T(\mu_T + K_4C^*)}T + \frac{\mu_U k_I}{\alpha_T(\mu_T + K_4C^*)}] \\ &-\mu_U k_I(\mu_B + K_3C^*)(K_1C^*+1)(1-T)(\alpha_T T + \mu_I + K_2C^*). \end{aligned} \tag{18}$$

Observe that

$$T^2 + \frac{\mu_U k_I + (\mu_T + K_4C^*)(\mu_I + K_2C^*)}{\alpha_T(\mu_T + K_4C^*)}T + \frac{\mu_U k_I}{\alpha_T(\mu_T + K_4C^*)} = (T-m)(T-n) \tag{19}$$

here we denote

$$\mathbb{B} = \frac{\mu_U k_I + (\mu_T + K_4C^*)(\mu_I + K_2C^*)}{\alpha_T(\mu_T + K_4C^*)}, \mathbb{C} = \frac{\mu_U k_I}{\alpha_T(\mu_T + K_4C^*)},$$

where

$$m = \frac{-\mathbb{B} + \sqrt{\mathbb{B}^2 + 4\mathbb{C}}}{2},$$

$$n = \frac{-\mathbb{B} - \sqrt{\mathbb{B}^2 + 4\mathbb{C}}}{2}.$$

It is clear that $n < 0$. Furthermore, from inequality $\mu_I \geq \mu_U$ we have $m \leq T_M$. Now, substituting equation (19) into equation (18), we can rewrite f as

$$\begin{aligned} f(T) = &-\alpha_T(\mu_T + K_4C^*)[r\beta - \gamma_U(\alpha_T T + \mu_I + K_2C^*)](T-m)(T-n) \\ &-\mu_U k_I(\mu_B + K_3C^*)(K_1C^*+1)(1-T)(\alpha_T T + \mu_I + K_2C^*). \end{aligned} \tag{20}$$

Table 1: Signs of the coefficients of equation (21).

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

Observe that

$$f(m) = -\mu_U k_I(\mu_B + K_3C^*)(K_1C^* + 1)(1 - m)(\alpha_T m + \mu_I + K_2C^*).$$

On the other hand, expanding f we obtain

$$f(T) = b_3T^3 + b_2T^2 + b_1T + b_0, \tag{21}$$

where

$$\begin{aligned}
b_3 &= (\mu_T + K_4C^*)\alpha_T^2\gamma_U,\\
b_2 &= \mu_U k_I\alpha_T[(\mu_B + K_3C^*)(K_1C^* + 1) + \gamma_U]\\
b_2 &= -(\mu_T + K_4C^*)\alpha_T[r\beta - 2\gamma_U(\mu_I + K_2C^*)],\\
b_1 &= -\mu_U k_I\alpha_T[(\mu_B + K_3C^*)(K_1C^* + 1) + \gamma_U]\\
&\quad -(\mu_I + K_2C^*)(\mu_T + K_4C^*)[r\beta - \gamma_U(\mu_I + K_2C^*)]\\
&\quad -\mu_U k_I\gamma_U(\mu_I + K_2C^*)(R_0 - 1)\\
b_2 &= -\mu_U k_I(\mu_I + K_2C^*)(\mu_B + K_3C^*)(R_0 - 1 - K_1C^*),\\
b_0 &= \mu_U k_I\gamma_U(\mu_I + K_2C^*)(R_0 - 1)\\
b_2 &= +\mu_U k_I(\mu_I + K_2C^*)(\mu_B + K_3C^*)(R_0 - 1 - K_1C^*).
\end{aligned}$$

Since $f(m) < 0$, and $f(0) = b_0 > 0$ for $R_0 > 1$, there exists at least one root T^* of f in the interval $(0, m)$. 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 Table 1. 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

$$r\beta - \gamma_U(\alpha_T T_M + \mu_I + K_2C^*) > r\beta - \gamma_U(\alpha_T T^* + \mu_I + K_2C^*) = 0,$$

which implies

$$
\begin{aligned}
f(\widetilde{T}) &= f(T_M) \\
&= -\alpha_T(\mu_T+K_4C^*)[r\beta-\gamma_U(\alpha_T T_M+\mu_I+K_2C^*)](T_M-m)(T_M-n) \\
&\quad -\mu_U k_I(\mu_B+K_3C^*)(K_1C^*+1)(1-T_M)(\alpha_T T_M+\mu_I+K_2C^*) \\
&< 0.
\end{aligned} \tag{22}
$$

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

$$f(\widetilde{T}) = f(T_M^*) = -\mu_U k_I(\mu_B+K_3C^*)(K_1C^*+1)(1-T_M^*)(\alpha_T T_M^*+\mu_I+K_2C^*) < 0.$$

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

Theorem 3.3. *For $R_0 < 1$, E_1 is locally asymptotically stable, and for $R_0 > 1$, E_1 is unstable.*

Proof. The Jacobian of system (3) evaluated at E_1 is

$$
J(E_1) = \begin{pmatrix}
-\mu_U - K_1C_{\max} & 0 & -\beta & 0 & -K_1 \\
0 & -\mu_I - K_2C_{\max} & \beta & 0 & 0 \\
0 & r & -(\gamma_U+\mu_B+K_3C_{\max}) & 0 & 0 \\
0 & k_I & 0 & -\mu_T - K_4C_{\max} & 0 \\
0 & 0 & 0 & 0 & -\eta
\end{pmatrix}.
$$

The characteristic polynomial of $J(E_1)$ is

$$
\begin{aligned}
p(\lambda) &= (\lambda+\mu_U+K_1C_{\max})(\lambda+\eta)(\lambda+\mu_T+K_4C_{\max}) \\
&\quad \times[\lambda^2+(\mu_I+K_2C_{\max}+\gamma_U+\mu_B+K_3C_{\max})\lambda \\
&\quad +(\mu_I+K_2C_{\max})(\gamma_U+\mu_B+K_3C_{\max})-r\beta].
\end{aligned} \tag{23}
$$

It is easy to see that three of the roots of (23) are $\lambda_1 = -\mu_U - K_1C_{\max} < 0$, $\lambda_2 = -\eta < 0$, $\lambda_3 = -\mu_T - K_4C_{\max} < 0$. In addition, the other two roots are determined by the following quadratic equation

$$
\begin{aligned}
&\lambda^2+(\mu_I+K_2C_{\max}+\gamma_U+\mu_B+K_3C_{\max})\lambda \\
&\quad +(\mu_I+K_2C_{\max})(\gamma_U+\mu_B+K_3C_{\max})(1-R_0) = 0.
\end{aligned} \tag{24}
$$

If $R_0 < 1$, then both roots of equation (24) have negative real part; and if $R_0 > 1$, then one of the roots of equation (24) has positive real part.

Therefore, E_1 is locally asymptotically stable for $R_0 < 1$, and E_1 is unstable for $R_0 > 1$. ■

In fact, we can prove the global stability of E_1 when $R_0 \le 1$.

Theorem 3.4. *If $R_0 \leq 1$, then E_1 is globally asymptotically stable.*

Proof. The Lyapunov function V can be defined as

$$V = rM_I + (\mu_I + K_2C)B, \tag{25}$$

which satisfies $V(x) \geq 0$ for all $x \in \Omega$. Taking the derivative of V along the solution of system (3), we can obtain

$$\begin{aligned}\frac{dV}{dt}\mid_{(3)} &= BM_U[r\beta - \gamma_U(\mu_I + K_2C)] - B(\mu_I + K_2C)(\mu_B + K_3C) - r\alpha_T M_I T \\ &\leq B(\mu_I + K_2C)(R_0 - 1)(\mu_B + K_3C + M_U) - r\alpha_T M_I T \\ &\leq 0,\end{aligned}$$

for all $x \in \Omega$, and the last inequality is obtained by the fact that $R_0 \leq 1$. From inspection of system (3) we can see that the maximum invariant set contained in the set $\{\frac{dV}{dt}\mid_{(3)} = 0\}$ is the plane $B = 0$, $M_I = 0$. In this set, system (3) becomes

$$\begin{cases} \dfrac{dM_U}{dt} = \mu_U - \mu_U M_U - K_1 C M_U, \\ \dfrac{dM_I}{dt} = 0, \\ \dfrac{dB}{dt} = 0, \\ \dfrac{dT}{dt} = -\mu_T T - K_4 C T, \\ \dfrac{dC}{dt} = -\eta C + C_M. \end{cases}$$

Which implies that the solutions starting there tend to the equilibrium E_1 as t goes to infinity. Therefore, by applying the LaSalle-Lyapunov Theorem (see [17]), we have that E_1 is globally asymptotically stable. ∎

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

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

where a_1 is a positive constant and

$$
\begin{aligned}
a_2 &= \left(\frac{\mu_U}{\beta B^* M_U^*}\frac{\mu_B}{\gamma_U}-1\right)a_1, \quad a_3=\frac{\mu_U}{\beta B^* M_U^*}\frac{\mu_B}{\gamma_U}a_1, \quad a_4=\frac{\mu_U}{\beta B^*}a_1 \\
a_5 &= \frac{\mu_U}{\gamma_U B^*}a_1, \quad a_6=\frac{\alpha_T T^* M_I^*}{k_I M_I^*(1-T^*)}\frac{\mu_U}{\beta B^*}\left(\frac{\mu_B}{\gamma_U M_U^*}+1\right)a_1, \quad a_7=a_1.
\end{aligned} \tag{26}
$$

We get some results as shown in the following theorems.

Theorem 3.5. *The derivative of V along the solutions of system (3) equals to $\frac{dV}{dt}\,|_{(3)}=-f$, where f is given by*

$$
\begin{aligned}
& f(x,y,z,u,v) \\
&= (a_1+a_2)\left[\mu_U M_U^*\left(x+\frac{1}{x}-2\right)+\beta B^* M_U^*\left(xz+\frac{1}{x}-z-1\right)\right] \\
&+(a_1+a_2)\left[K_1 C^* M_U^*\left(\frac{1}{x}-1\right)+K_1 C^* M_U^* M_U\left(\frac{1}{x}-1\right)+K_1 C M_U^*(x-1)\right] \\
&+(a_3+a_4)\left[\beta B^* M_U^*\left(\frac{xz}{y}+y-xz-1\right)+\alpha_T T^* M_I^*\left(yu+1-y-u\right)\right] \\
&+(a_3+a_4)\left[K_2 C^* M_I\left(\frac{1}{y}-1\right)+K_2 C M_I^*\left(y-1\right)\right] \\
&+a_5 r M_I^*\left(\frac{y}{z}+z-y-1\right)+a_5\gamma_U B^* M_U^*\left(xz+1-x-z\right) \\
&+a_5 K_3 C^* B^*\left(z-1\right)+a_5 K_3 C B\left(\frac{1}{z}-1\right) \\
&+a_6 k_I M_I^*\left(\frac{y}{u}+u-y-1\right)+a_6 k_I M_I^* T^*\left(uy+1-u-y\right) \\
&+a_6 K_4 C^* T^*\left(u-1\right)+a_6 K_4 C T\left(\frac{1}{u}-1\right)+a_7 C_M\left(\frac{1}{v}+v-2\right),
\end{aligned} \tag{27}
$$

and $x=M_U/M_U^*$, $y=M_I/M_I^*$, $z=B/B^*$, $u=T/T^*$, $v=C/C^*$.

Proof. Taking the derivative of V along the solutions of system (3), we will obtain

$$
\begin{aligned}
\frac{dV}{dt}\,|_{(3)} &= (a_1+a_2)\left(1-\frac{M_U^*}{M_U}\right)\left(\mu_U-\mu_U M_U-\beta B M_U-K_1 C M_U\right) \\
&+(a_3+a_4)\left(1-\frac{M_I^*}{M_I}\right)\left(\beta B M_U-\alpha_T T M_I-\mu_I M_I-K_2 C M_I\right) \\
&+a_5\left(1-\frac{B^*}{B}\right)\left(r M_I-\gamma_U B M_U-\mu_B B-K_3 C B\right) \\
&+a_6\left(1-\frac{T^*}{T}\right)\left[k_I(1-T)M_I-\mu_T T-K_4 C T\right] \\
&+a_7\left(1-\frac{C^*}{C}\right)\left(-\eta C+C_M\right).
\end{aligned} \tag{28}
$$

Form equations (7), we can get

$$\begin{aligned}
\mu_U &= \mu_U M_U^* + \beta B^* M_U^* + K_1 C^* M_U^*,\\
\mu_I &= \frac{\beta B^* M_U^*}{M_I^*} - \frac{\alpha_T T^* M_I^*}{M_I^*} - \frac{K_2 C^* M_I^*}{M_I^*},\\
\mu_B &= \frac{r M_I^*}{B_*} - \frac{\gamma_U B^* M_U^*}{B_*} - \frac{K_3 C^* B^*}{B^*},\\
\mu_T &= \frac{k_I M_I^*}{T^*} - \frac{k_I M_I^* T^*}{T^*} - \frac{K_4 C^* T^*}{T^*},\\
\eta &= \frac{C_M}{C^*},
\end{aligned}$$

and substituting these values of μ_U, μ_I, μ_B, μ_T and η into equation (28) we can obtain

$$\begin{aligned}
&\frac{dV}{dt}\,|_{(3)}\\
&= -(a_1{+}a_2)\left[\mu_U M_U^*\left(\frac{M_U}{M_U^*}{+}\frac{M_U^*}{M_U}{-}2\right){+}\beta B^* M_U^*\left(\frac{BM_U}{B^*M_U^*}{+}\frac{M_U^*}{M_U}{-}\frac{B}{B_*}{-}1\right)\right]\\
&-(a_1+a_2)\left[K_1 C^* M_U^*(1+M_U)\left(\frac{M_U^*}{M_U}-1\right)+K_1 C M_U^*\left(\frac{M_U}{M_U^*}-1\right)\right]\\
&-(a_3+a_4)\beta B^* M_U^*\left(\frac{BM_U M_I^*}{B^*M_U^*M_I}+\frac{M_I}{M_I^*}-\frac{BM_U}{B^*M_U^*}-1\right)\\
&-(a_3+a_4)\alpha_T T^* M_I^*\left(\frac{TM_I}{T^*M_I^*}+1-\frac{M_I}{M_I^*}-\frac{T}{T^*}\right)\\
&-(a_3+a_4)\left[K_2 C^* M_I\left(\frac{M_I^*}{M_I}-1\right)+K_2 C M_I^*\left(\frac{M_I}{M_I^*}-1\right)\right]\\
&-a_5 r M_I^*\left(\frac{B^*M_I}{BM_I^*}{+}\frac{B}{B^*}{-}\frac{M_I}{M_I^*}{-}1\right){-}a_5\gamma_U M_U^* B^*\left(\frac{M_U B}{M_U^* B^*}{+}1{-}\frac{B}{B^*}{-}\frac{M_U}{M_U^*}\right)\\
&-a_6 k_I M_I^*\left(\frac{T^*M_I}{TM_I^*}{+}\frac{T}{T^*}{-}\frac{M_I}{M_I^*}{-}1\right){-}a_6 k_I M_I^* T^*\left(\frac{TM_I}{T^*M_I^*}{+}1{-}\frac{T}{T^*}{-}\frac{M_I}{M_I^*}\right)\\
&-a_5 K_3 C^* B^*\left(\frac{B}{B^*}-1\right)-a_5 K_3 C B\left(\frac{B^*}{B}-1\right)\\
&-a_6 K_4 C^* T^*\left(\frac{T}{T^*}-1\right)-a_6 K_4 C T\left(\frac{T^*}{T}-1\right)-a_7 C_M\left(\frac{C}{C^*}+\frac{C^*}{C}-2\right).
\end{aligned} \tag{29}$$

If we denote

$$x = M_U/M_U^*, \quad y = M_I/M_I^*, \quad z = B/B^*, \quad u = T/T^*, \quad v = C/C^*,$$

then we get the result of this theorem. ∎

Theorem 3.6. *If $\gamma_U \le \mu_B$ and $R_0 > 1$, then the function f is nonnegative.*

Proof. In fact, we can obtain the constants defined in equation (26) by the following equalities

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

It is clear that $a_3, \cdots, a_7$, are positive, and we can get $a_2 > 0$, since $\gamma_U \leq \mu_B$. Substituting $rM_I^* = \gamma_U M_U^* B^* + \mu_B B^*$ and the equalities in equation (26) into the function f, we will get

$$\begin{aligned}
&f(x,y,z,u,v)\\
=\ & a_2\mu_U M_U^*\left(x+\frac{1}{x}-2\right) + (a_3+a_4)\beta B^* M_U^*\left(\frac{xz}{y}+\frac{y}{z}+\frac{1}{x}-3\right)\\
&+a_6 k_I M_I^* y\left(\frac{1}{u}+u-2\right) + a_7 C_M\left(\frac{1}{v}+v-2\right)\\
&+(a_1+a_2)K_1 C^* M_U^*(1+M_U)\left(\frac{1}{x}+x-2\right)\\
&+(a_3+a_4)K_2 C^* M_I\left(\frac{1}{y}+y-2\right) + a_5 K_3 C^* B^*\left(\frac{1}{z}+z-2\right)\\
&+a_6 K_4 C^* T^*\left(\frac{1}{u}+u-2\right),
\end{aligned} \tag{30}$$

Taking $d_1 = x$, $d_2 = y$, $d_3 = z$, $d_4 = u$ and $d_5 = v$ into the inequality $\sum_{i=1}^n d_i \geq n\sqrt[n]{\prod_{i=1}^n d_i}$, it is easy to see that the expressions inside the parenthesis of equation (30) are nonnegative, and therefore f is nonnegative. ■

Theorem 3.7. *If $\gamma_U \leq \mu_B$ and $R_0 > 1$, then the nontrivial equilibrium E_2 is globally asymptotically stable.*

Proof. It is clear that $V(E_2)=0$ and $V(x)\geq 0$ for all $x\in \text{int}\Omega$. Form Theorems 3.5 and 3.6, we have $\frac{dV}{dt}\ |_{(3)}= -f \leq 0$ for all $x \in \text{int}\Omega$. Further, we know that $\frac{dV}{dt}\ |_{(3)}= 0$ if and only if $M_U = M_U^*$, $M_I = M_I^*$, $B = B^*$, $T = T^*$ and $C = C^*$, which implies that all trajectories inside Ω will approach E_2 as t goes to infinity. This completes the proof. ■

4. Quadratic and Linear Optimal Control for System (2)

In this section, we will consider system (2) with quadratic and linear optimal control. By similar dimensional variables transformation as shown in section 3, the system (2) becomes to

$$
(31)\qquad \begin{cases} \dfrac{dM_U}{dt} &= \mu_U - \mu_U M_U - \beta B M_U - K_1 C M_U, \\ \dfrac{dM_I}{dt} &= \beta B M_U - \alpha_T M_I T - \mu_I M_I - K_2 C M_I, \\ \dfrac{dB}{dt} &= r M_I - \gamma_U M_U B - \mu_B B - K_3 C B, \\ \dfrac{dT}{dt} &= (1-T) k_I M_I - \mu_T T - K_4 C T, \\ \dfrac{dC}{dt} &= -\eta C + C_M(t). \end{cases}
$$

In the rest of this section, our target is to decrease the tuberculosis burden while minimizing the total drug administered. The effects of two different types of control strategies on system (31) are considered: (a) quadratic control, and (b) linear control.

4.1. Quadratic control strategy

In this subsection, we will consider the quadratic control. We will analyze the solution, which subjects to system (31) and it will minimize the following objective function

$$
(32)\qquad J(C_M(t)) = \int_0^{t_f} \left(B(t) + \frac{\epsilon}{2} C_M^2(t) \right) dt.
$$

Firstly, we can prove that there exists an optimal control that minimizes the objective function.

Theorem 4.1. (Existence of a Quadratic Optimal Control). *Given the objective function defined in* (32)*, where* $U = \{C_M(t)$ *piecewise continuous* $|0 \leq C_M(t) \leq 1,\ \forall t \in [0, t_f]\}$ *subject to system* (31) *with* $M_U(0) = M_{U_0}$, $M_I(0) = M_{I_0}$, $B(0) = B_0$, $T(0) = T_0$, $C(0) = C_0$ *then there exists an optimal control* C_M^* *such that* $\min_{C_M(t)\in[0,1]} J(C_M) = J(C_M^*)$ *if the following conditions are met:*

(1) *The class of all initial conditions with a control* $C_M(t)$ *in the admissible control set along with each state equation being satisfied is not empty.*

(2) *The admissible control set* U *is closed and convex.*

(3) *Each right hand side of the state system is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of* C_M *with coefficients depending on time and the state.*

(4) *The integrand of* $J(C_M)$ *is convex on* U *and is bounded below by* $-c_2 + c_1 C_M^2$ *with* $c_1 > 0$.

Proof. By the works of Fleming and Rishel [18], once we have proved the conditions 1 through 4 above, we get the existence of optimal control.

Since system (31) has bounded coefficients and the solutions are bounded on a finite time interval, we can use a result from Lukes [19] (Theorem 9.2.1, page 182), to obtain the existence of the solution of the system (31). Secondly we note that U is closed and convex by definition. For the third condition, the right hand side of system (31) must be continuous.

Let $\vec{\alpha}(t,\vec{X})$ be the right hand side of system (31) without $C_M(t)$ and let

$$\vec{f}(t,\vec{X},C_M)=\vec{\alpha}(t,\vec{X})+\begin{pmatrix}0\\0\\0\\0\\C_M\end{pmatrix},\qquad \vec{X}=\begin{pmatrix}M_U\\M_I\\B\\T\\C\end{pmatrix}.$$

By the boundedness of the solutions we get

$$\begin{aligned}&\left|\vec{f}(t,\vec{X},C_M)\right|\\ &\le\left|\begin{pmatrix}0&0&0&0&0\\ \frac{\beta B}{2}&0&\frac{\beta M_U}{2}&0&0\\ 0&r&0&0&0\\ 0&k_I&0&0&0\\ 0&0&0&0&0\end{pmatrix}\begin{pmatrix}M_U\\M_I\\B\\T\\C\end{pmatrix}\right|+\left|\begin{pmatrix}\mu_U\\0\\0\\0\\C_M\end{pmatrix}\right|\le A_1\Big(\left|\vec{X}\right|+|C_M|\Big),\end{aligned}\tag{33}$$

where A_1 depends on the coefficients of system (31).

For the fourth condition, we need to show

$$J(t,B,(1-p)u+pv)\le(1-p)J(t,B,u)+pJ(t,B,v).\tag{34}$$

By analyzing the difference of $J(t,B,(1-p)u+pv)$ and $(1-p)J(t,B,u)+pJ(t,B,v)$, we can see that

$$\begin{aligned}&J(t,B,(1-p)u+pv)-[(1-p)J(t,B,u)+pJ(t,B,v)]\\ &=B(t)+\frac{\epsilon}{2}(u^2-2pu^2+p^2u^2+p^2v^2-2p^2uv+2puv)\\ &-\Big(B(t)+\frac{\epsilon}{2}u^2-\frac{\epsilon}{2}u^2p+\frac{\epsilon}{2}pv^2\Big)\\ &=\frac{\epsilon}{2}(p^2-p)(u-v)^2.\end{aligned}$$

Since $p\in(0,1)$, it is easy to see that $(p^2-p)<0$. Together with $(u-v)^2>0$, we know that the expression $\frac{\epsilon}{2}(p^2-p)(u-v)^2$ is negative. This implies that $J(t,B,(1-p)u+pv)\le(1-p)J(t,B,u)+pJ(t,B,v)$.

Lastly,

$$B(t)+\frac{\epsilon}{2}C_M^2(t)\ge\frac{\epsilon}{2}C_M^2(t)\ge-c+\frac{\epsilon}{2}C_M^2(t),\tag{35}$$

which gives $-c + \frac{\epsilon}{2}C_M^2(t)$ as the lower bound. ■

With the existence of the quadratic optimal control established, we now characterize the optimal control using the Pontryagins Maximum Principle [20]. In the next theorem, we use $\frac{d\lambda_i}{dt} = \dot{\lambda}_i(t)$.

Theorem 4.2. *(Characterization of the Optimal Control). Given an optimal control C_M^* and solutions to the corresponding state system that minimize the function $J(C_M) = \int_0^{t_f}(B(t) + \frac{\epsilon}{2}C_M^2(t))dt$, there exist adjoint variables λ_i ($i = 1, 2, 3, 4, 5$) satisfying:*

$$\begin{cases} \dot{\lambda}_1 = \lambda_1(\beta B + \mu_U + K_1 C) - \lambda_2 \beta B + \lambda_3 \gamma_U B, \\ \dot{\lambda}_2 = \lambda_2(\alpha_T T + \mu_I + K_2 C) - \lambda_3 r - \lambda_4 k_I(1-T), \\ \dot{\lambda}_3 = \lambda_1 \beta M_U - \lambda_2 \beta M_U + \lambda_3(\gamma_U M_U + \mu_B + K_3 C) + 1, \\ \dot{\lambda}_4 = \lambda_2 \alpha_T M_I + \lambda_4(k_I M_I + \mu_T + K_4 T), \\ \dot{\lambda}_5 = \lambda_1 K_1 M_U + \lambda_2 K_2 M_I + \lambda_3 K_3 B + \lambda_4 K_4 T + \lambda_5 \eta, \end{cases} \tag{36}$$

where $\lambda_i(t_f) = 0$ for $i = 1, 2, 3, 4, 5$. Moreover, $C_M^*(t)$ can be represented by

$$C_M^*(t) = \min\left(1, \left(-\frac{\lambda_5}{\epsilon}\right)^+\right),$$

where the notation is

$$r^+ = \begin{cases} r \text{ if } & r \geq 0, \\ 0 \text{ if } & r < 0. \end{cases} \tag{37}$$

Proof. For the function $J(C_M)$, the Hamiltonian is given by

$$\begin{aligned} H = {} & B + \frac{1}{2}\epsilon C_M^2 + \lambda_1[\mu_U - \beta B M_U - M_U(\mu_U + K_1 C)] \\ & + \lambda_2[\beta B M_U - \alpha_T T M_I - M_I(\mu_I + K_2 C)] \\ & + \lambda_3[r M_I - \gamma_U M_U B - B(\mu_B + K_3 C)] \\ & + \lambda_4[k_I M_I(1-T) - T(\mu_T + K_4 C)] + \lambda_5(-\eta C + C_M). \end{aligned} \tag{38}$$

Since the control is bounded, we construct the Lagrangian as follows:

$$\mathrm{L} = H + W_1(t)C_M(t) - W_2(t)(1 - C_M(t)).$$

Here H is the Hamiltonian as defined in [21] and $W_i(t) \geq 0$ are penalty multipliers such that $W_1(t)C_M(t) = 0$ and $W_2(t)(1 - C_M(t)) = 0$ at the optimal C_M^*.

To characterize C_M^*, we analyze the necessary optimality condition $\frac{\partial \mathrm{L}}{\partial C_M} = 0$. Here, $\frac{\partial \mathrm{L}}{\partial C_M} = \frac{\partial H}{\partial C_M} + W_1 + W_2 = 0$ or $\epsilon C_M + \lambda_5 + W_1 + W_2 = 0$.

Using standard optimality arguments, we characterize the optimal control for $C_M(t)$ as

$$C_M^*(t) = \min\left(1, \left(-\frac{\lambda_5}{\epsilon}\right)^+\right).$$

We also note that the second derivative of the Lagrangian with respect to C_M is positive, so a minimum occurs at C_M^*. ■

4.2. Linear control strategy

For the same model (31), we now minimize an objective functional that is linear in the control,

$$J_1(C_M(t)) = \int_0^{t_f} (B(t) + \epsilon C_M(t))\, dt. \tag{39}$$

This objective functional depicts the situation of minimizing the tuberculosis cells and the total amount of drug given for a time interval $[0, t_f]$.

The existence of a linear control can be shown by techniques similar to those presented in Theorem 4.1. Assuming the existence of such a control, we will develop the characterization.

Theorem 4.3. (Characterization of the Optimal Control). *Given an optimal control $C_M^*(t)$, and solutions to the state equations that minimize the functional $J_1(C_M) = \int_0^{t_f}(B(t) + \epsilon C_M(t))dt$, there exist adjoint variables satisfying the adjoint Eq. (37) with $\lambda_i(t_f) = 0$ for $i = 1, 2, 3, 4, 5$. Further, the optimal control is characterized by*

$$C_M = \begin{cases} 0, & \text{if } \epsilon + \lambda_5 > 0, \\ 1, & \text{if } \epsilon + \lambda_5 < 0, \\ \frac{P}{Q}, & \text{if } \epsilon + \lambda_5 = 0, \end{cases}$$

where

$$\begin{aligned} Q &= K_3^2 B + \lambda_1(K_3^2 \beta B M_U - K_1^2 \mu_U) \\ &\quad + \lambda_2(2K_2K_3 r M_I + K_1^2 M_U \gamma_U - K_2^2 r M_I - K_3^2 r M_I - K_1 K_3 M_U \gamma_U), \\ P &= \dot{\lambda}_1 \xi_1 + \dot{\lambda}_2 \xi_2 + \lambda_1(\dot{\xi}_{11} + C\dot{E}) + \lambda_2(\dot{\xi}_{22} + C\dot{F}) + \dot{G} \\ &\quad - K_3^2 C(r M_I - M_U \gamma_U B - \mu_B B - K_3 C B) + \eta C Q. \end{aligned}$$

and the expression of ξ_1, ξ_2, ξ_{11}, ξ_{12}, ξ_{21}, ξ_{22}, E, F, G will been given in the proof.

Proof. In this case, the Hamiltonian of the system is given by

$$
\begin{aligned}
H \;=\; & B + \epsilon C_M + \lambda_1[\mu_U - \beta B M_U - M_U(\mu_U + K_1 C)] \\
& + \lambda_2[\beta B M_U - \alpha_T T M_I - M_I(\mu_I + K_2 C)] \\
& + \lambda_3[r M_I - \gamma_U M_U B - B(\mu_B + K_3 C)] \\
& + \lambda_4[k_I M_I(1 - T) - T(\mu_T + K_4 C)] + \lambda_5(-\eta C + C_M).
\end{aligned} \tag{40}
$$

The switching function in this case is $\phi = \frac{\partial H}{\partial C_M} = \epsilon + \lambda_5$. Since there is no explicit dependence on C_M in the switching function, the possibility of singular arcs arises.

The optimal control is given by

$$
C_M = \begin{cases} 0, & \text{if} \quad \epsilon + \lambda_5 > 0, \\ 1, & \text{if} \quad \epsilon + \lambda_5 < 0, \\ \text{Singular}, & \text{if} \quad \epsilon + \lambda_5 = 0. \end{cases}
$$

In the regions where the switching function is not zero, we have bang–bang control. In order to address the issue of singular arcs, we suppose the switching function is zero on an interval (t_1, t_2). This implies that all the derivatives of λ_5 must vanish in that interval. We can use this fact to determine the optimal control in such regions.

For the explanation to follow, we recall that $\dot{\lambda}_2$, $\dot{\lambda}_4$. Since $C(t) \geq 0$ and $\lambda_2(t_f) = 0$, $\lambda_4(t_f) = 0$, we can conclude that $\lambda_2(t) = 0$, $\lambda_4(t) = 0$ on the entire time interval. Setting the first three time derivatives of the switching function to zero, and using $\lambda_2 \equiv 0$, $\lambda_4 \equiv 0$, we obtain

$$
\begin{aligned}
\dot{\phi} &= 0 = \lambda_1 K_1 M_U + \lambda_3 K_3 B - \eta\epsilon, \\
\ddot{\phi} &= 0 = \lambda_1(K_1\mu_U + K_3\beta B M_U) + \lambda_3(K_1\gamma_U M_U - K_2 r M_I + K_3 r M_I) + K_3 B, \\
\dddot{\phi} &= 0 = \lambda_1\xi_1 + \lambda_2\xi_2 + K_1\gamma_U M_U - K_2 r M_I \\
&\qquad + K_3(2rM_I - \gamma_U M_U B - \mu_B B - K_3 C B),
\end{aligned}
$$

where

$$
\xi_1 = \xi_{11} + \xi_{12}, \quad \xi_2 = \xi_{21} + \xi_{22},
$$

$$
\begin{aligned}
\xi_{11} \;=\; & K_1\beta B\mu_U + K_1\beta\gamma_U M_U^2 + K_1\mu_U^2 - K_2 r\beta M_U M_I + 2K_3 r\beta M_U M_I \\
& - K_3 B\beta\gamma_U M_U^2 - K_3 B\beta\gamma_U M_U + K_3 B\beta\mu_U, \\
\xi_{12} \;=\; & (K_1^2\mu_U - K_3^2 B\beta M_U)C, \\
\xi_{21} \;=\; & K_1\gamma_U^2 M_U^2 + K_1\gamma_U M_U\mu_B + K_1\gamma_U\mu_U - K_1\gamma_U M_U B\beta - K_1\gamma_U M_U\mu_U \\
& + K_1 B\gamma_U\mu_U - K_2\gamma_U M_U r M_I - K_2\mu_B r M_I - K_2 r B\beta M_U + K_2 r\alpha_T T M_I \\
& + K_2 r M_I\mu_I + K_3\gamma_U M_U r M_I + K_3 B^2 r\beta\gamma_U M_U + K_3 r\mu_B M_I \\
& + K_3 r B\beta M_U - K_3 r\alpha_T M_I T - K_3 r\mu_I M_I, \\
\xi_{22} \;=\; & (K_1 K_3\gamma_U M_U - 2K_2 K_3 r M_I + K_3^2 r M_I - K_1^2\gamma_U M_U + K_2^2 r M_I)C.
\end{aligned}
$$

Denote

$$
\begin{aligned}
E &= K_1^2\mu_U - K_3^2 B\beta M_U,\\
F &= K_1K_3\gamma_U M_U - 2K_2K_3rM_I + K_3^2 rM_I - K_1^2\gamma_U M_U + K_2^2 rM_I,\\
G &= K_1\gamma_U M_U - K_2 rM_I + K_3(2rM_I - \gamma_U M_U B - \mu_B B).
\end{aligned}
$$

From $\dot{\phi} = 0$ and $\ddot{\phi} = 0$, we can get

$$
\begin{aligned}
\lambda_1 &= \frac{\eta\epsilon}{K_1M_U} - \frac{K_3B[\eta\epsilon(K_1\mu_U+K_3B\beta M_U)+K_3BK_1M_U]}{K_1M_U[K_3BK_1\mu_U+K_3^2B^2\beta M_U-K_1^2\gamma_U M_U^2+K_1K_2rM_UM_I-K_1K_3rM_IM_U]},\\
\lambda_3 &= \frac{\eta\epsilon(K_1\mu_U+K_3B\beta M_U)+K_3BK_1M_U}{K_3BK_1\mu_U+K_3^2B^2\beta M_U-K_1^2\gamma_U M_U^2+K_1K_2rM_UM_I-K_1K_3rM_IM_U}.
\end{aligned}
$$

Now, we know all the five adjoint variables in terms of the state in a singular region. To determine the control, we need to find the fourth derivative of the switching function.

We see that $\dddot{\phi} = 0 = P - QC_M$ or $C_M = \frac{P}{Q}$, where

$$
\begin{aligned}
Q &= K_3^2B + \lambda_1(K_3^2\beta BM_U - K_1^2\mu_U)\\
&\quad +\lambda_2(2K_2K_3rM_I + K_1^2M_U\gamma_U - K_2^2rM_I - K_3^2rM_I - K_1K_3M_U\gamma_U),\\
P &= \dot{\lambda}_1\xi_1 + \dot{\lambda}_2\xi_2 + \lambda_1(\dot{\xi}_{11} + C\dot{E}) + \lambda_2(\dot{\xi}_{22} + C\dot{F}) + \dot{G}\\
&\quad -K_3^2C(rM_I - M_U\gamma_U B - \mu_B B - K_3CB) + \eta CQ.
\end{aligned}
$$

For the singular control to be minimizing, the Generalized Legendre Clebsch condition needs to be satisfied, that is Q would have to be non-negative on this interval. Note that Q is only negative in a very specific region. In this region, we can guarantee that there are no singular minimizing arcs, so the control is bang–bang. In other regions, the potential for singular arcs has not been ruled out. In fact, it will arise in most practical situations, since most of the $T - N$ plane meets the criterion $Q \geq 0$. ■

5. Conclusion

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 with chemotherapy. In terms of drug delivery, we considered two cases: (a)in system (1), the input rate of chemotherapy drug is constant, C_M, and (b) in system (31), the input rate of chemotherapy drug is changeable $C_M(t)$.

In section 3, we analyze the existence and stability of equilibria of system (1). We get the basic reproduction number R_0 in equation (6). From Theorem 3.2, we know that if $R_0 \leq 1$, then equilibrium E_1 is the only equilibrium in Ω; if $R_0 > 1$, besides E_1, there exists an endemic equilibrium E_2. By Theorem 3.4, we get that E_1 is globally asymptotically stable provided that $R_0 \leq 1$, which means that the infected macrophage and Mtb bacteria cells will be ultimately eradicated. However, by Theorem 3.7, we

know that the nontrivial equilibrium E_2 is globally asymptotically stable provided that $\gamma_U \leq \mu_B$ and $R_0 > 1$, which means that infected macrophage and Mtb bacteria cells will be persist for all the time. In this case, we can control the Mtbs by choose a suitable C_M, such that the equilibrium value less then the threshold.

In section 4, two kinds of optimal control strategies are considered. In the quadratic control case, we established the existence and characterization of quadratic optimal control by Theorems 4.1 and 4.2. In the linear optimal control case, by assumption of existence, we established the characterization of the linear control in Theorem 4.3. In this case, our theoretical results show that singular control is possible.

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. 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.

This paper also involve the use of two immune cell populations included in the dynamics to reduce the TB burden, the qualitative results for quadratic and linear optimal control scenarios. The quadratic and linear controls have similar behavior in the administration of the chemotherapy drug. They are both turned on at full power for a short period of time, then they are essentially turned off. In the linear control it is completely turned off. However in the quadratic case, the control quickly moves to a small value, then gradually decreases. Since the amount of drug being delivered to the patient is small, the quadratic control treatment is comparable to the linear bang–bang control case in that the Mtb is reduced by the same magnitude over the same time frame. However, the quadratic control has the added benefit of keeping the Mtb in check when it is small. When the Mtb is small, the strongest treatment of the Mtb is unnecessary. The quadratic control allows for a weaker treatment that minimizes the harmful side effects while allowing the system to maintain a low Mtb size.

Using a murine model, Sköld et al [22] 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 [23, 24] 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. In future work, mathematical models that include the role of these cells in the immune response should be considered. Investigations into more complex models will address the ability of combined immunotherapy and chemotherapy to control the

TB burden and hopefully to eradicate the bacteria.

REFERENCES

1. WHO Report, *Global Tuberculosis Control-Surveillance*, Planning, Financing, 2008.
2. J. Palomino, S. Cardoso and V. Ritacco, Tuberculosis 2007-From basic science to patient care, http://www.Tuberculosistextbook.com, 2007.
3. J. Chan and J. Flynn, The immunological aspects of latency in tuberculosis, *Clin. Immunol.*, **110** (2004), 2-12.
4. A. Gallegos, E. Pamer and M. Glickman, Delayed protection by ESAT-6-specific effector $CD4^+$ T cells after airborne M. tuberculosis infection, *J. Exp. Med.*, **205** (2008), 2359-2368.
5. T. Ulrischs and S. Kaufmann, *Cell Mediated Immune Response in Tuberculosis*, Lippincott Williams and Wilkins, New York, 2004.
6. E. Ibarguen-Mondragon, L. Esteva and L. Chávez-Galán, A mathematical model for cellular immunology of tuberculosis, *Math Biosci Eng.*, **8** (2011), 973-986.
7. Centers for disease control and prevention, TB elimination-the difference between latent TB infection and TB disease, 2010, Available from: http://www.cdc.gov/tb/publications/factsheets/general/LTBIandActiveTB.pdf.
8. J. Davis and L. Ramakrishnan, The role of the granuloma in expansion and dissemination of early tuberculous infection, *Cell*, **136** (2007), 37-49.
9. M. Tsai, S. Chakravarty, G. Zhu, J. Xu, K. Tanaka, C. Koch, J. Tufariello, J. Flynn and J. Chan, Characterization of the tuberculous granuloma in murine and human lungs: Cellular composition and relative tissue oxygen tension, *Cell Microbiol.*, **8** (2006), 218-232.
10. J. Wigginton and D. Kischner, A model to predict cell mediated imune regulatory mechanisms during human infection with Mycobacterium tuberculosis, *J. Immunol.*, **166** (2001), 1951-1967.
11. S. Marino and D. Kirschner, The human immune response to the Mycobacterium tuberculosis in lung and lymph node, *J. Theor. Biol.*, **227** (2004), 463-486.
12. D. Kirschner, D. Sud, C. Bigbee and J. L. Flynn, Contribution of $CD8^+T$ cells to control of mycobacterium tuberculosis infection, *J. Immuno.*, **176** (2006), 4296-4314.
13. G. Magombedze, W. Garira and E. Mwenje, Modelling the human immune response mechanisms to Mycobacterium tuberculosis infection in the lungs, *Math. Biosci. Eng.*, **3** (2006), 661-682.
14. A. Swierniak, U. Ledzewicz and H. Schattler, Optimal control for a class of compartmental models in cancer chemotherapy, *J. Appl. Math. Comput. Sci.*, **13** (2003), 357-368.
15. L. G. de Pillis, W. Gu, K. R. Fister, T. Head, K. Maples, A. Murugan, T. Neal and K. Yoshida, Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls, *Math. Biosci.*, **209** (2007), 292-315.

16. U. Ledzewicz, T. Brown and H. Schattler, Comparison of optimal controls for a model in cancer chemotherapy with L_1 and L_2 type objectives, *Optim. Meth. Software*, **19** (2004), 339-350.

17. J. Hale, *Ordinary Differential Equations*, Wiley, New York, 1969.

18. W. H. Fleming and R. W. Rishel, *Deterministic and Stochastic Optimal Control*, Springer-Verlag, 1975.

19. D. L. Lukes, *Differential Eequations: Classical to Controlled*, Vol. 162, Academic Press, 1982.

20. L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze and E. F. Mishchenko, The mathematical theory of optimal processes, Gordon and Breach, 1962.

21. K. A. Chester, A. Mayer, etc., Recombinant anti-carcinoembryonic antigen antibodies for targeting cancer, *Cancer Chemother. Pharmacol.*, **46** (2000), s8-12.

22. M. Sköld and S. M. Behar, Tuberculosis triggers a tissue-dependent program of differentiation and acquisition of effector functions by circulating monocytes, *J. Immuno.*, **81** (2008), 6349-6360.

23. A. J. Wolf, B. Linas, etc., Mycobacterium tuberculosis infects dendritic cells with high frequency and impairs their function *in vivo*, *J. Immunol.*, **179** (2007), 2509-2519.

24. M. Anis, S. Fulton, etc, Modulation of pulmonary dendritic cell function during mycobacterial infection, *Infect. Immun.*, **76** (2008), 671-677.

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