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Simple mathematical models on macrophages and CTL responses against Mycobacterium tuberculosis

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Abstract. In this work we formulate fourth mathematical models trying to describe basic aspects into the dynamics of the *Mycobacterium tuberculosis* (Mtb) infection at different stages. The purpose of this study is to evaluate the impact of the response of T cells and macrophages in the control of Mtb.

Keywords. Mathematical model, Tuberculosis, Stability, Immunology, Equilibrium solutions.

Resumen. En este trabajo se formulan cuatro modelos matemáticos que intentan describir aspectos básicos de la dinámica de la infección con el *Micobacterium tuberculosis* (Mtb) en diferentes etapas. El propósito de este estudio es evaluar el impacto de la respuesta de las células T y los macrófagos en el control del Mtb.

Palabras Clave. Modelo matemático, Tuberculosis, Estabilidad, Inmunología, soluciones de equilibrio

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]. In most cases the initial infection progresses to a

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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 immune response that occurs after 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 [5].
Mathematical models have been applied to understand the celular immunology of TB. Among them we have R. Antia et. al. [6], D. Kirschner [7, 8], Magombedze et al. [9, 10], E. Ibargen-Mondragn et al. [11, 12, 13, 14, 15, 16, 17, 18, 19], Alavez et al. [20], Baloni et al [21], Shi et al. [22], Bru and Cardona [23], Yang [24], Guirado and Schlesinger [25], Carvalho [26], Goutelle et al. [27], E. Pienaar and M. Lerm [28]
In this paper we are interested in modeling the interaction of immune system cells more relevant in the immunology of TB (macrophages and T cells) together with the Mtb at different stages of infection. To this end, we formulate and analyze a sequence of four mathematical models. The first model describes the interaction of macrophages and bacteria at the beginning of the infection. The second model describes the interaction of macrophages and bacteria in the context of innate immunology of TB. The third model describes the interaction of macrophages, T cells and bacteria. In this case the cytotoxic response of T cells is stimulated by the inability of macrophages controlling the infection progress. The fourth model is a combination between the previous two in which both macrophages and T cells have the capacity to fight against the bacteria. This model is found within the cell mediated immunology of TB.

1 The basic model of Mtb infection dynamics

Infection with *Mycobacterium tuberculosis* (Mtb) follows a relatively well-defined process. The infectious bacilli are inhaled as droplets from the atmosphere. In the lung the bacteria are phagocytosed by alveolar macrophages and induce a localized proinflammatory response that leads to the recruitment of mononuclear cells from neighboring blood vessels [29].
Since macrophages are the first targets of the bacteria we formulate a mathematical model about Mtb infection dynamics considering the following population; uninfected macrophages, infected macrophages, Mtb bacteria which are denoted by x, y, and b, respectively. We assume that uninfected macrophages reproduce at constant rate λ, and die at a per capita constant rate μ. Uninfected macrophages become infected at a rate proportional to the product of x and b, with constant of proportionality β. Infected macrophage die at per capita constant rate ν, where $\nu \geq \mu$. Mtb bacteria multiply inside infected macrophages up to a limit at which the macrophage bursts, and releases bacteria. For this reason, we assume that infected macrophages produce Mtb bacteria at a rate proportional to the population, ρy. Infected macrophages die at a rate νy and Mtb bacteria are removed from the system at a rate γb. The above assumptions lead to the following system of nonlinear differential equations

$$\begin{aligned} x' &= \lambda - \mu x - \beta x b \\ y' &= \beta x b - \nu y \\ b' &= \rho y - \gamma b. \end{aligned} \tag{1.1}$$

The set of biological interest is given by

$$\Omega = \left\{(x, y, b) \in (\mathbb{R}_0^+)^3 : 0 \leq x + y \leq \lambda/\mu, 0 \leq b \leq \lambda\rho/\gamma\mu\right\}. \tag{1.2}$$

The following lemma ensures that the system (1.1) has biological sense, that is, all solutions starting in Ω remain there for all $t \geq 0$.

Lemma 1.1. *The set Ω defined in (1.2) is positively invariant for the solutions of the system (1.1).*

Proof. We begin adding the first two equations of (1.1) and using the fact that $\nu \geq \mu$ we obtain

$$\frac{d}{dt}(x+y) + \mu(x+y) \leq \lambda. \tag{1.3}$$

From (1.3) we see that

$$x(t) + y(t) \leq \frac{\lambda}{\mu} + \left(-\frac{\lambda}{\mu} + x_0 + y_0\right) e^{-\mu_U t},$$

where $x_0 + y_0 \leq \lambda/\mu$, which implies $x(t) + y(t) \leq \lambda/\mu$ for all $t \geq 0$. Similarly it is proved that $0 \leq b(t) \leq \lambda\rho/\gamma\mu$. On the other hand, it can be easily verified that the vector field defined by (1.1) points to the interior of Ω. Therefore the solutions starting in Ω remain there for all $t \geq 0$. ☑

A similar model was formulated by M. Nowak and R. May [30] for virus dynamics. This is not a coincidence because although bacteria and viruses are very different microorganisms, in the infection process Mtb behaves like a virus. Nowak's model has been widely studied and used. Its qualitative analysis was made by Li and Muldowney [31], Leenheer and Smith [32], Korobeinikov [33]. The qualitative analysis of the model (1.1) is given in terms of *basic reproductive number* R_0 which is

$$R_0 = \frac{\beta\lambda\rho}{\mu\nu\gamma}. \tag{1.4}$$

This number is interpreted as the number of secondary infections that arises from a macrophage during its lifetime when all other macrophages are uninfected. The results of existence and stability of equilibrim solutions are summarized in the following propositions.

Proposition 1.2. *If $R_0 \leq 1$, then the infection-free equilibrium $E_0 = (\lambda/\mu, 0, 0)$ is the only equilibrium of system (1.1). If $R_0 > 1$, in addition to E_0 there exists an endemic equilibrium E_1 given by*

$$E_1 = \left(\frac{\nu\gamma}{\beta\rho}, (R_0 - 1)\frac{\mu\gamma}{\beta\rho}, (R_0 - 1)\frac{\mu}{\beta}\right).$$

Proposition 1.3. *If $R_0 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable, and the infection cannot persist. If $R_0 > 1$, the endemic equilibrium E_1 is globally asymptotically stable, and the infections persists indefinitely.*

For the proofs of above propositions see [31] or [32].

2 The basic model of Mtb infection dynamics with macrophages response

The innate immune system acts at the early phase as the front line for host defense against Mtb infection. At this stage, different immune system cells such as neutrophils, mast cells, macrophages, dendritic cells and natural killer trying to stop the progression of bacteria through different effector mechanisms. The innate immune response against Mtb infection is so complex that at present there are still many questions about it. However, the scientific community agrees that the main effector cells in this response are the macrophages. For this reason, in this section we will explore the innate immune response induced by effector mechanisms of macrophages.

As mentioned earlier, in the lung the bacteria are phagocytosed by alveolar macrophages that often destroy them. At this stage, the Mtb destruction depends on the intrinsic microbicidal capacity of host phagocytes and virulence factors of the ingested Mtb bacteria [34]. When bacteria evades their elimination, they multiply inside an infected macrophage up to a limit at which the macrophage bursts, and releases bacteria. When this happens, macrophages induce a localized proinflammatory response that leads to the recruitment of mononuclear cells from neighboring blood vessels.
In this section we want to make a model on innate response against Mtb. To this end, the Mtb bacteria replicates according to the basic model of Mtb infection dynamics (1.1). The innate response or macrophages response kill bacteria at proportional rate to the product of x and b with constant of proportionality ψ. The innate response rate ψ including the effects of rate at which uninfected macrophages eliminate bacteria, and effector mechanisms involved in the killing of mycobacteria such that apoptosis. Under the previously described assumptions, we obtain the following mathematical model

$$\begin{aligned} x' &= \lambda - \mu x - \beta x b \\ y' &= \beta x b - \nu y \\ b' &= \rho y - \psi x b - \gamma b. \end{aligned} \tag{2.1}$$

For this system we have that the following invariance result.

Lemma 2.1. *The set Ω defined in (1.2) is positively invariant for the solutions of the system (2.1).*

Proof. Similarly to proof of Lemma 1.1. ☑

2.1 Equilibrium solutions

In this section we will characterize the equilibrium solutions of the system (2.1). Before infection, the system is at the equilibrium state $x = \lambda/\mu$, $y = 0$, and $b = 0$. Suppose that bacteria enter to the organism. The infection progression will depend of the *basic reproductive number,* R_1, defined by

$$R_1 = \frac{\beta\rho\lambda}{\mu\nu\,(\gamma + \gamma')}, \tag{2.2}$$

where $\gamma' = \psi\lambda/\mu$ is the rate at which bacteria are eliminated by innate response at its equilibrium level. The following proposition summarizes the existence results of the equilibria.

Proposition 2.2. *If $R_1 \leq 1$, then $P_0 = (\lambda/\mu, 0, 0)$ is the only equilibrium in Ω. If $R_1 > 1$, in addition to P_0, there exists an endemic equilibrium P_1.*

Proof. Equilibrium solutions of (2.1) are given by solutions of the following algebraic system

$$\begin{aligned} \lambda - \mu x - \beta x b &= 0 \\ \beta x b - \nu y &= 0 \\ \rho y - \psi x b - \gamma b &= 0, \end{aligned} \tag{2.3}$$

which are infection-free equilibrium $P_0 = (\lambda/\mu, 0, 0)$ and endemic equilibrium $P_1 = (x_1, y_1, b_1)$ where

$$\begin{aligned} x_1 &= \frac{\lambda}{\mu + \beta b_1} \\ y_1 &= \frac{\beta\lambda b_1}{\nu(\mu + \beta b_1)} \\ b_1 &= \frac{(\mu\gamma + \psi\lambda)(R_1 - 1)}{\gamma\beta}. \end{aligned}$$

☑

2.2 Stability of equilibrium solutions

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

Proposition 2.3. *If $R_1 < 1$, then P_0 is locally asymptotically stable, and unstable when $R_1 > 1$,.*

Proof. To analyze the local stability of the equilibrium P_0 we will use the Jacobian of the system (2.1) which is given by

$$J = \begin{pmatrix} -(\mu+\beta b) & 0 & -\beta x \\ \beta b & -\nu & \beta x \\ -\psi b & \rho & -(\psi x+\gamma) \end{pmatrix}. \tag{2.4}$$

The eigenvalues of the Jacobian (2.4) evaluated at P_0 are given by $-\mu$, and the solutions of the quadratic equation

$$\xi^2 + \left(\nu + \psi\frac{\lambda}{\mu} + \gamma\right)\xi - \nu\left(\gamma + \psi\frac{\lambda}{\mu}\right)(R_1 - 1) = 0. \tag{2.5}$$

From Routh-Hurwitz criteria we conclude that the roots of the equation (2.5) have negative real part if and only if $R_1 < 1$ (see [35]). ☑

Actually, we can prove global stability of P_0 when $R_1 \leq 1$.

Proposition 2.4. *If $R_1 \leq 1$ then P_0 is globally asymptotically stable.*

Proof. The function U defined by

$$U = \rho y + \nu b, \tag{2.6}$$

satisfies $U(P_0) = 0$ and $U(P) \geq 0$ for all $P \in \Omega$. Since $R_1 \leq 1$ implies $\rho\beta - \nu\psi < \mu\nu\gamma/\lambda$, then its orbital derivative satisfies

$$\dot{U} = (\rho\beta - \nu\psi)xb - \nu\gamma b \leq \frac{\mu\nu\gamma}{\lambda}xb - \nu\gamma b = \frac{\mu\nu\gamma}{\lambda}b\left(x - \frac{\lambda}{\mu}\right) \leq 0.$$

In consequence $\dot{U}(P) \leq 0$ for all $P \in \Omega$. From inspection of system (2.1) we can see that the maximum invariant set contained in the set $\dot{U} = 0$ is the line $y = 0$, $b = 0$. In this set, system (2.1) becomes

$$x' = \lambda - \mu x, \quad y' = 0, \quad b' = 0.$$

Which implies that the solutions starting there tend to equilibrium P_0 as t goes to infinity. Therefore, applying the LaSalle-Lyapunov Theorem (see [35]) we have that P_0 is globally asymptotically stable. ☑

Now, we are going to prove the stability of P_1.

Proposition 2.5. *If $R_1 > 1$, then P_1 is locally asymptotically stable*

Proof. From equilibrium equations (2.3) we have

$$\mu + \beta b_1 = \frac{\lambda}{x_1}, \; \psi x_1 + \gamma = \frac{\rho y_1}{b_1}. \tag{2.7}$$

Substituting the equations (2.7) in the Jacobian (2.4) we obtain

$$J(P_1) = \begin{pmatrix} -\frac{\lambda}{x_1} & 0 & -\beta x_1 \\ \beta b_1 & -\nu & \beta x_1 \\ -\psi b_1 & \rho & -\frac{\rho y_1}{b_1}. \end{pmatrix}. \tag{2.8}$$

The characteristic polynomial of $J(P_1)$ in (2.8) is given by

$$p(\xi) = \xi^3 + a_1\xi^2 + a_2\xi + a_3, \tag{2.9}$$

where

$$\begin{aligned} a_1 &= \nu + \frac{\rho y_1}{b_1} + \frac{\lambda}{x_1} \\ a_2 &= \nu\frac{\lambda}{x_1} + \nu\frac{\rho y_1}{b_1} + \gamma\beta b_1 \\ a_3 &= \gamma\nu\beta b_1. \end{aligned}$$

The Routh-Hurwitz criterion states that the roots of the polynomial p defined in (2.9) have negative real part if and only if $a_i > 0$ and $\Delta_2 = a_1a_2 - a_3 > 0$ for $i = 1, 2, 3$. It is clear that $a_i > 0$ for $i = 1, 2, 3$. After some simplifications we obtain

$$\Delta_2 = \nu\left(\nu\frac{\lambda}{x_1} + \mu\frac{\rho y_1}{b_1}\right) + \left(\nu + \mu\frac{\rho y_1}{b_1} + \frac{\lambda}{x_1}\right)\left(\nu\frac{\lambda}{x_1} + \mu\frac{\rho y_1}{b_1} + \gamma\beta b_1\right) > 0.$$

Therefore, P_1 is locally asymptotically stable. ☑

Now, we are going to prove from direct method of Lyapunov that P_1 is globally asymptotically stable when $\gamma \geq \gamma'$. For this end, we use the following Lyapunov function

$$\begin{aligned} V &= a_1\left[x - x_1 - x_1\ln\left(\frac{x}{x_1}\right)\right] + a_2\left[y - y_1 - y_1\ln\left(\frac{y}{y_1}\right)\right] \\ &\quad + a_3\left[b - b_1 - b_1\ln\left(\frac{b}{b_1}\right)\right], \end{aligned}$$

where a_3 is a positive constant and

$$a_1 = \frac{\gamma}{\beta x_1}a_3,\ a_2 = \frac{\rho y_1}{\beta x_1 b_1}a_3. \tag{2.10}$$

To prove the global stability of P_1 using Lyapunov's direct method we have to show that $V(P) > 0$ and $\dot{V}(P) < 0$ for all $P \in \Omega$. To this end, we need the results given in next propositions.

Proposition 2.6. *The orbital derivative of V is $\dot{V} = -f$ where f is given by*

$$\begin{aligned} f &= a_1\mu x_1\left(w_1 + \frac{1}{w_1} - 2\right) + a_1\beta x_1 b_1\left(w_1w_3 + \frac{1}{w_1} - w_3 - 1\right) \\ &\quad + a_2\beta x_1 b_1\left(\frac{w_1w_3}{w_2} + w_2 - w_1w_3 - 1\right) + a_3\rho y_1\left(\frac{w_2}{w_3} + w_3 - w_2 - 1\right) \\ &\quad + a_3\psi x^+b^+(w_1w_3 + 1 - w_3 - w_1), \end{aligned} \tag{2.11}$$

being $w_1 = x/x_1$, $w_2 = y/y_1$, and $w_3 = b/b_1$.

Proof. The orbital derivative of V is given by

$$\begin{aligned}\dot{V} &= a_1\left(1-\frac{x_1}{x}\right)(\lambda-\mu x-\beta x b)+a_2\left(1-\frac{y_1}{y}\right)(\beta x b-\nu y)\\ &\quad +a_3\left(1-\frac{b_1}{b}\right)(\rho y-\psi x b-\gamma b)\end{aligned} \tag{2.12}$$

From the equilibrium equations (2.3) we have

$$\lambda=\mu x_1+\beta x_1 b_1,\ \nu=\frac{\beta x_1 b_1}{y_1},\ \gamma=\frac{\rho y_1}{b_1}-\frac{\psi x_1 b_1}{b_1}. \tag{2.13}$$

Replacing above values of λ, ν, and γ in (2.12) we obtain

$$\begin{aligned}\dot{V} &= -a_1\mu x_1\left(\frac{x}{x_1}+\frac{x_1}{x}-2\right)+a_1\beta x_1 b_1\left(\frac{xb}{x_1 b_1}+\frac{x_1}{x}-\frac{b}{b_1}-1\right)\\ &\quad -a_2\beta x_1 b_1\left(\frac{xby_1}{x_1 b^{+}y}+\frac{y}{y_1}-\frac{xb}{x_1 b_1}-1\right)-a_3\rho y_1\left(\frac{b_1 y}{by_1}+\frac{b}{b_1}-\frac{y}{y_1}-1\right)\\ &\quad -a_3\psi x_1 b_1\left(\frac{xb}{x_1 b_1}+1-\frac{b}{b_1}-\frac{x}{x_1}\right).\end{aligned}$$

In the variables $w_1=x/x_1$, $w_2=y/y_1$ and $w_3=b/b_1$ we have $\dot{V}=-f$. ☑

Proposition 2.7. *If $\gamma\geq\gamma'$, then the function f is nonnegative.*

Proof. Since

$$\begin{aligned}a_1\mu x_1-a_3\psi x_1 b_1 &= \left(\frac{\gamma\mu}{\beta}-\psi x_1 b_1\right)a_3\\ &= \left(\frac{\gamma\mu^2+\mu\beta(\gamma-\gamma')b_1}{\beta(\mu+\beta b_1)}\right)a_3\\ &> 0,\end{aligned}$$

implies $a_1\mu x_1>a_3\psi x_1 b_1$ and $w_1+1/w_1-2=(w_1-1)^2/w_1\geq 0$, then f satisfies

$$\begin{aligned}f &\geq a_3\psi x_1 b_1\left(w_1+\frac{1}{w_1}-2\right)+a_1\beta x_1 b_1\left(w_1w_3+\frac{1}{w_1}-w_3-1\right)\\ &\quad +a_2\beta x_1 b_1\left(\frac{w_1w_3}{w_2}+w_2-w_1w_3-1\right)+a_3\rho y_1\left(\frac{w_2}{w_3}+w_3-w_2-1\right)\\ &\quad +a_3\psi x_1 b_1(w_1w_3+1-w_3-w_1)\\ &= (a_3\psi x_1 b_1+a_1\beta x_1 b_1)\left(w_1w_3+\frac{1}{w_1}-w_3-1\right)\\ &\quad +a_2\beta x_1 b_1\left(\frac{w_1w_3}{w_2}+w_2-w_1w_3-1\right)+a_3\rho y_1\left(\frac{w_2}{w_3}+w_3-w_2-1\right).\end{aligned}$$

From next equalities

$$a_3\psi x_1 b_1+a_1\beta x_1 b_1 = a_2\beta x_1 b_1 = a_3\rho y_1$$

we obtain the constants defined in (2.10) and the function f satisfies

$$f(w_1,w_2,w_3)\geq a_3\rho y_1\left(\frac{w_1w_3}{w_2}+\frac{w_2}{w_3}+\frac{1}{w_1}-3\right), \tag{2.14}$$

Taking $d_1=w_1w_2/w_3$, $d_2=w_2/w_3$, and $d_3=1/w_1$ 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 expression inside parenthesis of (2.14) is nonnegative, and therefore f is nonnegative. ☑

Theorem 2.8. *If $R_1 > 1$ and $\gamma \geq \gamma'$ then nontrivial equilibrium P_1 is globally asymptotically stable.*

Proof. It is clear that $V(P_1) = 0$ and $V(P) \geq 0$ for all $P \in \Omega$. From Proposition 2.6 we have $\dot{V} = -f$ and from Proposition 2.7 we have f is nonnegative, therefore $\dot{V}(P) \leq 0$ for all $P \in \Omega$. Further $\dot{V} = 0$ if and only if $x = x_1$, $y = y_1$, and $b = b_1$ which implies all trajectories inside Ω approach P_1 when t goes to infinity. ☑

3 The basic model of Mtb infection dynamics with CTL response

As mentioned in the introduction, Mtb targets macrophages. When macrophages fail to harm Mtb, several T-cells populations are required for the successful control of the pathogen. In this section we want to make a model of cytotoxic T cells (CTL) response against Mtb. To this end, the Mtb bacteria replicates according to the basic model of Mtb dynamics (1.1). Let us explore the effect of a CTL response, c, which provides a maximum amount of CTL for the purpose of eliminating infected macrophages.
In the presence of bacteria and infected macrophages, the supply of specific T-cells is given by $\sigma\left(1 - c/c_{max}\right) y$, where σ is the recruitment rate of T cells, and c_m is the maximum T cell population level. Finally, the T-cells die at per capita rate δ.
The assumptions above lead to the following system of nonlinear differential equations

$$\begin{aligned} x' &= \lambda - \mu x - \beta x b \\ y' &= \beta x b - \alpha y c - \nu y \\ b' &= \rho y - \gamma b \\ c' &= \sigma\left(1 - \frac{c}{c_m}\right) y - \delta c. \end{aligned} \tag{3.1}$$

In this case, the set of biological interest is given by

$$\Omega_1 = \left\{(x, y, b, c) \in (\mathbb{R}_0^+)^4 : 0 \leq x + y \leq \lambda/\mu, 0 \leq b \leq \lambda\rho/\gamma\mu, 0 \leq c \leq \lambda\sigma/\delta\mu\right\}. \tag{3.2}$$

The following lemma ensures that system (3.1) has biological sense, that is, all solutions starting in (3.2) remain there for all $t \geq 0$.

Lemma 3.1. *The set Ω_1 defined in (3.2) is positively invariant for the solutions of the system (3.1).*

Proof. Similarly to the proof of Lemma 1.1. ☑

3.1 Equilibrium Solutions

In this case, before infection, the system is at the equilibrium $x = 1$, $y = 0$, $b = 0$, and $c = 0$. Suppose that bacteria enter to the organism. The infection progression will depend of the *basic reproductive number*, R_0, defined in (1.4). The following theorem summarizes the existence results of the equilibria.

Proposition 3.2. *If $R_0 \leq 1$, then $\bar{P}_0 = (\lambda/\mu, 0, 0, 0)$ is the only equilibrium in Ω. If $R_0 > 1$, in addition to $\bar{P}_0$, there exists an infected equilibrium*

$$P_2 = \left(\frac{\lambda}{\mu + \beta b_2}, \frac{\gamma}{\rho} b_2, b_2, \frac{c_m \sigma \gamma b_2}{\gamma b_2 + c_m \delta \rho}\right).$$

See [13] for proof of Proposition 3.2.

3.2 Stability of equilibrium solutions

In this section we analyze the stability of equilibria. We begin with the stability analysis of the infection-free equilibrium.

Proposition 3.3. *For $R_0 < 1$, $\bar{P}_0$ is locally asymptotically stable, and for $R_0 > 1$, $\bar{P}_0$ is unstable.*

See [13] for proof of Proposition 3.3. Actually, we can prove global stability of $\bar{P}_0$ when $R_0 \leq 1$.

Proposition 3.4. *If $R_0 \leq 1$ then $\bar{P}_0$ is globally asymptotically stable.*

See [13] for proof of Proposition 3.4. In the following we will prove the asymptotic stability of $\bar{P}_1$ when $R_0 > 1$. For this, we use the following Lyapunov function

$$\begin{aligned} V &= a_1\left[x - x_2 - x_2\ln\left(\frac{x}{x_2}\right)\right] + a_2\left[y - y_2 - y_2\ln\left(\frac{y}{y_2}\right)\right] \\ &\quad + a_3\left[b - b_2 - b_2\ln\left(\frac{b}{b_2}\right)\right] + a_4\left[c - c_2 - c_2\ln\left(\frac{c}{c_2}\right)\right], \end{aligned}$$

where a_1 is a positive constant and

$$a_2 = a_1,\ a_3 = \frac{\beta b_2 x_2 a_1}{\rho y_2},\ a_4 = \frac{\alpha c_2 y_2 a_1}{\sigma y_2(1 - c_2/c_m)}. \tag{3.3}$$

As above, next results are needed for prove stability.

Proposition 3.5. *The orbital derivative $\dot{V}$ of V is equal to $\dot{V} = -f$ where f is given by*

$$\begin{aligned} f &= a_1\left[\mu x_2\left(w_1 + \frac{1}{w_1} - 2\right) + \beta x_2 b_2\left(w_1 w_3 + \frac{1}{w_1} - w_3 - 1\right)\right] \\ &\quad + a_2\left[\beta x_2 b_2\left(\frac{w_1 w_3}{w_2} + w_2 - w_1 w_3 - 1\right) + \alpha y_2 c_2(1 + w_2 w_4 - w_2 - w_4)\right] \\ &\quad + a_3\rho y_2\left(\frac{w_2}{w_3} + w_3 - w_2 - 1\right) \\ &\quad + a_4\sigma y_2\left(\frac{w_2}{w_4} + w_4 - w_2 - 1\right) + a_4\frac{\sigma}{c_m} y_2 c_2(w_2 w_4 + 1 - w_2 - w_4), \end{aligned} \tag{3.4}$$

where $w_1 = x/x_2$, $w_2 = y/y_2$, $w_3 = b/b_2$ and $w_4 = c/c_2$.

See [13] for proof of Proposition 3.4.

Proposition 3.6. *The function f is nonnegative.*

See [13] for proof of Proposition 3.6.

Theorem 3.7. *If $R_0 > 1$ then nontrivial equilibrium E_2 is globally asymptotically stable.*

See [13] for proof of Theorem 3.7.

4 The basic model of Mtb infection dynamics with macrophage and CTL responses

In this section we formulate a model that consider both the innate and CTL response. The model is formulated from the macrophage response model (section 3) and the model for

CTL response (section 4). Under the same hypotheses of the previous models we obtain the following system of ordinary differential equation

$$\begin{aligned} x' &= \lambda - \mu x - \beta x b \\ y' &= \beta x b - \alpha y c - \nu y \\ b' &= \rho y - \psi x b - \gamma b \\ c' &= \sigma \left(1 - \frac{c}{c_m}\right) y - \delta c. \end{aligned} \tag{4.1}$$

The results of existence and stability of equilibrium solutions are given in terms of the basic reproductive number R_1 define in (2.2), which are summarized in next propositions.

Proposition 4.1. *If $R_0 \leq 1$, then $Q_1 = (\lambda/\mu, 0, 0, 0)$ is the only equilibrium of the system (4.1). If $R_0 > 1$, in addition to Q_1, there exists an infected equilibrium, $Q_2 = (x, y, b, c)$.*

Proposition 4.2. *If $R_0 \leq 1$ then Q_1 is globally asymptotically stable.*

Proposition 4.3. *If $\gamma' \leq \gamma$ then nontrivial equilibrium Q_2 is globally asymptotically stable when $R_1 > 1$.*

For the proofs of above propositions see [11].

5 Numerical solutions

To make the graphs in Figure 1 were used the following parameter values σ=0.08, c_m=50000, δ=0.33, ρ=0.12, ψ=0.0000002, γ=0.012, β=0.0000001, α=0.00002, ν=0.02, λ=1000, and μ=0.01. For these values we obtain $R_0 = 5$ and $R_1 = 1.875$, which implies that the population of bacteria can not be eliminated in any case. Figure 1 confirm the above, in

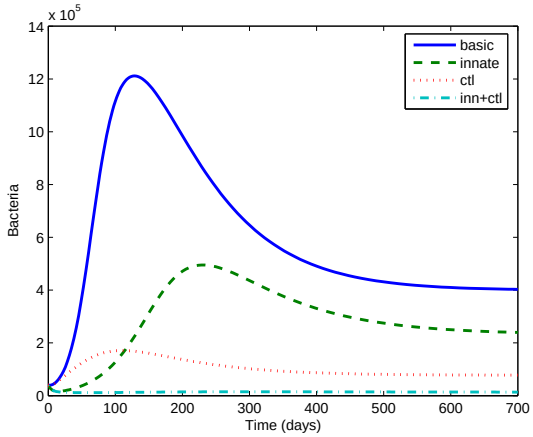

Figure 1: Bacterial growth in all models.

the first 100 days of the infection, the innate response is more efficient than the cytotoxic response in the control of bacteria progression. However, in the course of the time the cytotoxic response becomes a more effective response. These results are consistent with different reports which state that in the early stage of infection the innate response is more relevant than the cellular response mediated by T lymphocytes. Also, we find that some results state that the main protective response to the outcome of Mtb infection is mediated cellular consisting of T cells and different effector mechanisms [34, 4, 3].

6 Discussion

In this work we formulate four mathematical models that attempt to describe the dynamics of Mycobacterium tuberculosis infection at different stages. These models consider the interaction of the most relevant cell populations in the TB infection (macrophages, T cells and bacteria). The qualitative analysis of the models is given in terms of the basic reproductive numbers R_0 and R_1 given by

$$R_0 = \frac{\beta\lambda\rho}{\mu\nu\gamma},\ R_1 = \frac{\beta\lambda\rho}{\mu\nu(\gamma+\gamma')}, \tag{6.1}$$

where $\gamma' = \psi\dfrac{\lambda}{\mu}$ is the rate at which bacteria are eliminate by innate response at its equilibrium level. Observe that

- R_0 is the basic reproductive number of the basic model (1.1) and the basic model with cytotoxic response (3.1).
- R_1 is the basic reproductive number of the basic model with innate response (2.1) and basic model with both responses (4.1).

Since $R_1 \leq R_0$ then the results suggest that the onset of infection, the innate response is more efficient than the cytotoxic response. As shown in Figure 1, the best model to control the bacterial growth is one that combines both the innate response as well as the cytotoxic response.

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