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Research article

On macrophage response to primary *Mycobacterium tuberculosis* in humans

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Abstract: Tuberculosis stands as the leading cause of death worldwide, driven by infection from a single bacterial agent, and has been recognized as a global public health concern by the World Health Organization. Recent studies highlight that the innate immune response has a central role in controlling the initial spread of *Mycobacterium tuberculosis* (Mtb) within the host, and triggers adaptive immune response. We developed and analyzed a model examining the interactions among macrophages, innate cells, and Mtb to determine whether the infection is controlled by the innate immune response or whether a specific adaptive response is triggered. Findings suggest that if an individual infected by Mtb has an adequate immunological state to prevent bacteria from infecting the macrophage population (that is, if the external bacteria engulfed by macrophages are eliminated by them, or if their capacity to replicate inside them is limited), then the innate immune response will effectively control the primary infection.

Keywords: tuberculosis; innate immune response; within-host model; ordinary differential equation; qualitative analysis; normalized sensitivity index

1. Introduction

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* (Mtb). The World Health Organization has declared it a significant threat to humanity, accounting for approximately two million deaths each year. TB ranks as one of the leading causes of death

worldwide from a single infectious agent, surpassing HIV/AIDS [1]. Primary infection is defined as the initial infection of a host by a pathogen that has completed a dormant period, and for which the host has no existing antibodies [1].

Progression of primary Mtb infection may lead to pulmonary and pleural complications (such as tuberculous pneumonia, hyperinflation, and collapse/consolidation), pleural effusion, and disseminated disease. Primary tuberculosis occurs mainly in children, but is increasingly seen in adults, and it is usually a mild illness that is often not recognized [2].

The outcome of primary infection is determined by the interaction of Mtb with soluble and cellular components of the innate immune system, essentially with alveolar macrophages, which are its natural phagocytic agents [3], as well as the interactions of other immune and non-immune cells in the lungs, and the role of non-cellular components [4].

A confrontation is presented, in which the host must balance the inflammatory response to limit damage to lung tissue, while simultaneously inducing an immune response sufficient to control the infection. In contrast, Mtb must overcome the initial defensive barriers present in the mucosa, or in the respiratory tract to access the pulmonary alveoli, where it will encounter phagocytic cells such as alveolar macrophages [3].

The body's defense mechanisms against substances perceived as harmful or foreign are classified into innate and acquired immune responses. The role of adaptive or acquired immunity in controlling Mtb infection is well studied and the protective function of T and B lymphocytes in anti-tuberculosis immunity is widely recognized. However, there are still important gaps in our understanding of Mtb pathogenesis and host mechanisms [5]. In this regard, it is of vital importance to advance in the understanding of the dynamics of interaction between pathogen and host, mainly in the pulmonary microenvironment, because this is the initial and primary site of infection, where unique challenges arise for both the host and the pathogen [6].

Transmission of Mtb begins when an infected individual expels microdroplets containing the infectious bacillus into the environment, which are then inhaled by an uninfected person. Infectious bacilli can survive for up to 3 hours in closed, non-ventilated spaces. Those that overcome the intrinsic barriers of the innate immune response (skin, mucous membranes, tears) enter the respiratory tract, which serves as a means of transport, generally to the pulmonary alveoli [7].

While many cells of the innate immune system are involved in the response to TB, the precise mechanisms of TB immunopathology remain not fully understood. Among the innate cells involved in the primary TB are alveolar epithelial cells, alveolar macrophages, neutrophils, endothelial cells, eosinophils, dendritic cells, inflammatory monocytes, natural killer cells, and innate lymphoid cells, among others [6]. It is well documented that macrophages are the primary innate immune cells responding to Mtb, but they also serve as a niche for Mtb replication and propagation. Recent studies have shown that other cells, such as dendritic cells, neutrophils, and monocytes, also play a critical role in the immunopathology of TB [8].

In this article, we aim to contrast the role of the macrophage response with that of other innate immune cells during primary Mtb infection. In this context, mathematical models have been utilized to gain insights into the within-host dynamics of TB, particularly in relation to adaptive immunity [9–12]. It is now understood that the innate immune response is crucial to the outcome of primary Mtb infection, as it can control bacterial progression and significantly influence the host's subsequent adaptive response.

In the literature, we find works that analyze several aspects of the innate immune response against Mtb throughout of mathematical modeling. Pedruzzi et al. [13], formulated a system of ordinary differential equations that describes the interaction dynamics between Mtb, iron, lipids, and nitric oxide in the early phase of macrophage infection. They incorporated the bactericidal property of nitric oxide and the cellular regulation of iron and lipids to analyze the role they play in the outcome of infection.

Gammack et al. [14] developed a spatiotemporal model of the initial and innate response to TB. The model consists of coupled reaction-diffusion-advection equations governing the dynamics of macrophages (resting and infected), bacteria (extracellular and intracellular), and a chemokine released by the bacteria, each of which affects final granuloma size. The model describes the migration of uninfected macrophages to the site of infection (pulmonary alveoli) and their subsequent phagocytosis of bacteria. It aims to capture clearance by innate immunity or disease progression through granuloma growth. Clarelli and Natalini [15] modeled the early immune response to Mtb infection in the lungs by means of coupled reaction-diffusion-transport equations with chemotaxis. The results and conclusions are similar to those presented by Gammack et al. [14]. There are other computational approaches that address the role of early innate immunity in TB [13, 16–18].

2. Formulation of the mathematical model

In this section, we will formulate a mathematical model that describes the interaction dynamics between innate immune cells and Mtb at the site of infection. For this purpose, we group all the innate immune cells that act in the innate response against Mtb into a single population, which we will denote as C.

These cells differentiate into various groups of effector cells, particularly into macrophages, which we will denote as M. These macrophages are categorized into uninfected macrophages, M_U, which have not encountered Mtb or effectively eliminate it after phagocytosis, and infected macrophages (M_I), which is phagocytose cell but lacks the capacity to eliminate Mtb, allowing bacteria to reproduce within them.

Similarly, we define the population of bacteria, B, which is divided in two subpopulations: internal bacteria, B_I, which have been phagocytosed by innate cells, and external bacteria, B_E, which have not been phagocytosed or have transitioned from internal to external due to the necrotic death of their host cells. We assume that the site of infection is the pulmonary alveoli, where infectious bacilli have been transported. At this location, resident cells, along with those recruited from the bone marrow via the thymus or lymph nodes, have initiated an innate immune response.

As mentioned in the previous section, the range of cells involved in this response is quite broad. However, at this stage of the infection, none of these cells exhibit a specific response to the antigen. In this context, the population of cells involved in primary TB at time t is represented by $C(t)$. This population includes subgroups of alveolar epithelial cells, endothelial cells, macrophages, neutrophils, eosinophils, monocytes, dendritic cells, natural killer cells, invariant natural killer T lymphocytes, and innate lymphoid cells, among others.

Immune system cells originate in the bone marrow, which is estimated to produce between 200 and 500 billion new blood cells each day. These cells migrate to several organs, such as the thymus and lymph nodes, where they give rise to the main types of immune cells, including monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, dendritic cells, platelets, T cells, B

cells, and natural killer cells, among others [19]. This information allows us to assume that immune cells derived from stem cells are recruited at a constant rate, denoted as Λ_C, and die a per capita natural death rate μ_C.

The process that begins with the production of stem cells in the bone marrow and involves the transition to other cell types—such as the differentiation of promonocytic cells into mature monocytes—includes homeostasis with self-regulation mechanisms, among other factors, until mature macrophages capable of executing their effector functions against pathogens, particularly Mtb, are formed. We refer to this process as the differentiation of bone marrow cells into mature macrophages [20]. In this context, we assume that innate cells differentiate into uninfected macrophages at a per capita constant rate α.

It is important to note that the dynamics of interaction between uninfected macrophages and external bacteria lead to the formation of two new populations. Specifically, when uninfected macrophages phagocytize external bacteria, these bacteria are transferred to the internal bacteria compartment. Additionally, macrophages that cannot totally eliminate the phagocytized bacteria and instead allow them to reproduce within themselves become classified as infected macrophages [6]. Based on the above, we will assume that uninfected macrophages phagocytose Mtb at a rate ε, generating new infected macrophages at a rate ν.

After phagocytosis, non-pathogenic internal bacteria are degraded through the acidification of the phagosomal compartment [21]. Based on the above, we assume that internal bacteria are eliminated by uninfected macrophages at a constant rate, denoted as θ. As mentioned earlier, stem cells also differentiate into other innate cells, such as dendritic cells and neutrophils, which can phagocytose and eliminate Mtb, as well as B lymphocytes that produce antibodies against Mtb, among other innate cells. In the model, this innate cell response against Mtb is represented by a constant elimination rate of external bacteria, denoted as η.

In primary tuberculosis, programmed cell death of macrophages plays a crucial role in host immunopathology. When it is confronted with a pathogen that uses the host's cellular resources for survival and replication, one defensive strategy is to activate programmed cell death (apoptosis) in the host cell [22]. Apoptosis is a highly regulated process of cellular dismantling that confines the cytoplasmic contents of dying cells within membrane-bound vesicles known as apoptotic bodies, effectively sealing all cellular contents within these bodies. The apoptosis of infected cells can benefit the host in several ways, including the silent elimination of these cells [22]. Given that different innate cells produce substances (cytokines) that induce apoptosis in infected macrophages, we assume that this response occurs at a constant rate λ.

To promote bacterial progression, Mtb inhibits apoptosis and induces unprogrammed cell death, known as necrosis, through protein pathways that stimulate the production of mitochondrial reactive oxygen species (ROS) [23]. Additionally, necrotic macrophages become a niche for Mtb replication before the bacteria are released into the extracellular environment [6]. Based on the above, we will assume that the necrosis of infected macrophages occurs at a per capita constant rate ρ. On the other hand, we will assume that infected macrophages release bacteria into the outside environment at the average rate r.

In this model, we assume that internal bacteria replicate inside infected macrophages, according to

the Monod kinetics at a specific growth rate given by

$$\frac{\mu N}{K_m + N}, \tag{2.1}$$

where N is the concentration of the nutrient, μ the maximum specific growth rate of B_I inside M_I, and K_m is the Monod constant or half-saturation constant (nutrient concentration at which the specific growth rate reaches half of its maximum). Since infected macrophages provide the nutrients required for Mtb replication, we assume that N is proportional to M_I, with a positive proportionality constant σ; that is, $N = \sigma M_I$. Substituting the above equation in (2.1), we obtain

$$\frac{\mu\sigma M_I}{K_m + \sigma M_I}.$$

Finally, since all cells have an average life span, we will denote by μ_{MU}, μ_{MI}, μ_{BE}, and μ_{BI}, the natural deaths of uninfected macrophages, infected macrophages, external and internal bacteria, respectively.

From the above assumptions, a flow diagram is presented in Figure 1, and the following system of ordinary differential equations is deduced

$$\begin{aligned}
\frac{dC}{dt} &= \Lambda_C - \alpha C - \mu_C C,\\
\frac{dM_U}{dt} &= \alpha C - \varepsilon\nu B_E M_U - \mu_{MU} M_U,\\
\frac{dM_I}{dt} &= \varepsilon\nu B_E M_U - \lambda M_I C - \rho M_I - \mu_{MI} M_I,\\
\frac{dB_E}{dt} &= r\rho M_I - \eta B_E C - \mu_{BE} B_E,\\
\frac{dB_I}{dt} &= \varepsilon B_E M_U + \frac{\mu\sigma M_I B_I}{K_m + \sigma M_I} - \theta B_I M_U - \mu_{BI} B_I.
\end{aligned} \tag{2.2}$$

Let

$$\mu_M = \min\{\mu_{MU}, \mu_{MI}\},\ \mu_B = \min\{\mu_{BE}, \mu_{BI}\},\ C^* = \frac{\Lambda_C}{\alpha + \mu_C}, \mathbb{R}_+ = [0, \infty), \tag{2.3}$$

then the following set

$$\Omega = \left\{ \begin{pmatrix} C \\ M_U \\ M_I \\ B_E \\ B_I \end{pmatrix} \in \mathbb{R}^5_+ : 0 \le C \le C^*, 0 \le M_U + M_I \le \frac{\alpha C^*}{\mu_M} \right\} \tag{2.4}$$

is our set of biological interest. In fact, the following lemma ensures that all solutions of system (2.2), starting at Ω, remain there for all $t \ge 0$.

Lemma 2.1. *Set Ω defined in (2.4) is positively invariant for solutions of system (2.2).*

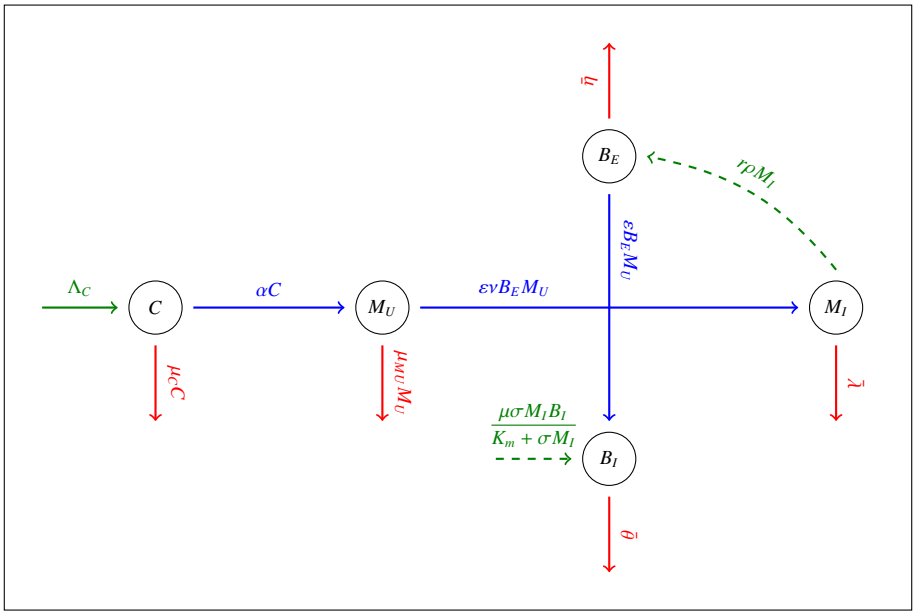

Figure 1. Flow diagram of system (2.2). The blue arrows indicate transitions between compartments. Solid green lines represent external sources to the system, while dashed green lines indicate internal supply sources. Red lines indicate outputs from the compartment outside the system. $\bar{\lambda} = \lambda M_I C + \rho M_I + \mu_{MI} M_I$, $\bar{\eta} = \eta B_E C + \mu_{BE} B_E$, $\bar{\theta} = \theta B_I M_U + \mu_{BI} B_I$.

Proof. Let us start by verifying the existence of solutions to the initial value problem defined by system (2.2) and initial condition

$$x_0 = (C(0), M_U(0), M_I(0), B_E(0), B_I(0)) \in \Omega.$$

Since the vector field defined by the right hand side of (2.2) is $C^1(\mathbb{R}^5_+)$, then the fundamental theorem of existence and uniqueness guarantees the existence of a solution $x(t) \in \mathbb{R}^5_+$ in the interval $[0, \sigma]$ [24]. Furthermore, if the compact set $\bar{\Omega} \in \mathbb{R}^5_+$ satisfies $\{y \in \mathbb{R}^5 : y = f(t) \text{ for some } t \in [0, \sigma)\}$, then by the extension theorem, $\sigma = \infty$ ([24], Corolario 2, pg 91). Now, suppose that $x_0 \in \Omega$, and we have

$$0 \le C(0) \le \frac{\Lambda_C}{\alpha + \mu_C}, 0 \le M_U(0) + M_I(0) \le \frac{\alpha}{\mu_M}, 0 \le B_E(0) + B_I(0) \le \frac{\bar{\alpha}}{\mu_B}.$$

On the other hand, the solution of the first equation of system (2.2) is given by

$$C(t) = \frac{\Lambda_C}{\alpha + \mu_C} + \left(C(0) - \frac{\Lambda_C}{\alpha + \mu_C} \right) e^{-\mu_C t},$$

since $0 \le C(0) \le \Lambda_C/(\alpha + \mu_C)$, and then $0 \le C(t) \le \Lambda_C/(\alpha + \mu_C)$ for all $t \ge 0$. Adding the second and third equations of system (2.2), we have

$$\frac{d}{dt}(M_U + M_I) = \alpha C - (\lambda M_I C + \rho M_I + \mu_{MU} M_U + \mu_{MI} M_I).$$

Since $\mu_M < \mu_{MU}$ and $\mu_M < \mu_{MI}$, then from the previous equation, we obtain the following inequality:

$$\frac{d}{dt}(M_U + M_I) < \frac{\alpha \Lambda_C}{\alpha + \mu_C} - \mu_M (M_U + M_I).$$

The solution of the above inequality satisfies

$$M_U(t) + M_I(t) < \frac{\alpha\Lambda_C}{\mu_U(\alpha+\mu_C)} + \left(M_U(0) + M_I(0) - \frac{\alpha\Lambda_C}{\mu_M(\alpha+\mu_C)}\right)e^{-\mu_M t},$$

since $0 \le M_U(0) + M_I(0) \le \dfrac{\alpha\Lambda_C}{\mu_M(\alpha+\mu_C)}$, and then $0 \le M_U(t) + M_I(t) \le \dfrac{\alpha\Lambda_C}{\mu_M(\alpha+\mu_C)}$ for all $t \ge 0$.

It remains to be shown that on the boundary of Ω ($\partial\Omega$), the solutions of system (2.2) point towards its interior. Now, let us define $x = (C, M_U, M_I, B_E, B_I)^T \in \mathbb{R}^5$ and $f(x) = (f_1(x), \ldots, f_5(x))^T$ as the right-hand side of the system (2.2), then the above system can be rewritten as

$$x' = f(x), \tag{2.5}$$

together with suitable initial conditions $x(0) = x_0 \in \mathbb{R}^5_+$. It can be readily verified that, whenever $x(0) \in \mathbb{R}^5_+$ with $x_i = 0$, for $i = 1, \ldots, 5$, then $f_i(x)|_{x_i=0} \ge 0$. Due to the Lemma of Nagumo (1942), any solution of (2.5) with $x_0 \in \mathbb{R}^5_+$, say $x(t) = x(t, x_0)$, is such that $x(t) \in \mathbb{R}^5_+$ for all $t > 0$ [25]. Thus, all solutions are positively invariant.

3. Qualitative analysis of the model

3.1. Equilibrium solutions

Setting the right-hand side of (2.2) equal to the zero vector gives the following system of algebraic equations:

$$\begin{aligned}
\Lambda_C - \alpha C - \mu_C C &= 0,\\
\alpha C - \varepsilon\nu B_E M_U - \mu_{MU} M_U &= 0,\\
\varepsilon\nu B_E M_U - \lambda M_I C - \rho M_I - \mu_{MI} M_I &= 0, \qquad (3.1)\\
r\rho M_I - \eta B_E C - \mu_{BE} B_E &= 0,\\
\varepsilon B_E M_U + \frac{\mu\sigma M_I B_I}{K_m + \sigma M_I} - \theta B_I M_U - \mu_{BI} B_I &= 0. \qquad (3.2)
\end{aligned}$$

From the first equation of (3.1), we obtain $C = C^*$. Substituting C^* defined in (2.3) in the second equation of (3.1), we obtain

$$M_U = \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}}. \tag{3.3}$$

From the third equation of (3.1), we obtain

$$\begin{aligned}
M_I &= \frac{\varepsilon\nu B_E M_U}{\lambda C^* + \rho + \mu_{MI}}\\
&= \frac{\varepsilon\nu B_E}{\lambda C^* + \rho + \mu_{MI}} \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}}.
\end{aligned} \tag{3.4}$$

Substituting C^* defined in (2.3), (3.3), and (3.4) in the fourth equation of (3.1), we obtain

$$r\rho \frac{\varepsilon\nu B_E}{\lambda C^* + \rho + \mu_{MI}} \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}} - (\eta C^* + \mu_{BE}) B_E = 0.$$

The solutions of above equation are given by $B_E = 0$ and $B_E = B_E^*$, where

$$B_E^* = \frac{\mu_{MU}}{\varepsilon\nu}(R_0 - 1), \tag{3.5}$$

being

$$R_0 = \frac{r\rho\varepsilon\nu\alpha C^*}{(\lambda C^* + \rho + \mu_{MI})\mu_{MU}(\eta C^* + \mu_{BE})}. \tag{3.6}$$

If $B_E = 0$, we obtain the free-infection equilibrium

$$E_0 = \left(C^*, \frac{\alpha C^*}{\mu_{MU}}, 0, 0, 0\right). \tag{3.7}$$

Now, by substituting (3.5) in (3.3) and (3.4), we obtain

$$\begin{aligned} M_U^* &= \frac{\alpha C^*}{\mu_{MU} R_0}, \\ M_I^* &= \frac{(R_0 - 1)\alpha C^*}{(\lambda C^* + \rho + \mu_{MI})R_0}. \end{aligned} \tag{3.8}$$

Solving for B_I from the fifth equation of (3.1), we obtain

$$B_I = \frac{\varepsilon B_E M_U}{\mu_{BI} + \theta M_U - \dfrac{\mu\sigma M_I}{K_m + \sigma M_I}}.$$

Substituting (3.5), and (3.8) in the above equation, after some calculations, we obtain

$$\begin{aligned} B_I &= \frac{K_m R_0(\lambda C^* + \rho + \mu_{MI}) + \sigma(R_0 - 1)\alpha C^*}{\nu\mu\sigma R_0(R_1 - 1)} \\ &= \frac{\mu_{MU}(R_0 - 1)\alpha C^* R_1}{\nu(\mu_{BI}\mu_{MU} R_0 + \theta\alpha R_0)(R_1 - 1)}, \end{aligned}$$

where

$$R_1 = \frac{(\mu_{BI}\mu_{MU} R_0 + \theta\alpha C^*)[K_m R_0(\lambda C^* + \rho + \mu_{MI}) + \sigma(R_0 - 1)\alpha C^*]}{\mu_{MU}\mu\sigma R_0(R_0 - 1)\alpha C^*}. \tag{3.9}$$

In consequence, if $R_0 > 1$ and $R_1 > 1$, there exists a non-trivial equilibrium

$$E_1 = (C^*, M_U^*, M_I^*, B_E^*, B_I^*). \tag{3.10}$$

The following theorem summarizes the results of the existence of equilibria.

Teorem 3.1. *System (2.2) always has the free-infection equilibrium $E_0 \in \Omega$ defined in (2). If $R_0 > 1$ and $R_1 > 1$, in addition to E_0, there exists the infected equilibrium $E_1 \in \Omega$ defined in (4).*

3.2. Stability of equilibrium solutions

In this section we discuss the local stability of the equilibrium solutions of (2.2). The linearization of the system (2.2) around an equilibrium solution $\bar{x}$ is given by $x' = J(\bar{x})x$, where the jacobian matrix J evaluated at x is given by

$$J(x) = \begin{pmatrix} -(\alpha+\mu_C) & 0 & 0 & 0 & 0 \\ \alpha & -(\varepsilon\nu B_E + \mu_{MU}) & 0 & -\varepsilon\nu M_U & 0 \\ -\lambda M_I & \varepsilon\nu B_E & -(\lambda C + \rho + \mu_{MI}) & \varepsilon\nu M_U & 0 \\ -\eta B_E & 0 & r\rho & -(\eta C + \mu_{BE}) & 0 \\ 0 & \varepsilon B_E - \theta B_I & \dfrac{\mu\sigma K_m B_I}{(K_m+\sigma M_I)^2} & \varepsilon M_U & \dfrac{\mu\sigma M_I}{K_m+\sigma M_I} - \theta M_U - \mu_{BI} \end{pmatrix}. \tag{3.11}$$

From (3.11), we verify that the Jacobian matrix evaluated in trivial equilibrium E_0 is given by

$$J(E_0) = \begin{pmatrix} -(\alpha+\mu_C) & 0 & 0 & 0 & 0 \\ \alpha & -\mu_{MU} & 0 & -\dfrac{\varepsilon\nu\alpha C^*}{\mu_{MU}} & 0 \\ 0 & 0 & -(\lambda C^* + \rho + \mu_{MI}) & \dfrac{\varepsilon\nu\alpha C^*}{\mu_{MU}} & 0 \\ 0 & 0 & r\rho & -(\eta C^* + \mu_{BE}) & 0 \\ 0 & 0 & 0 & \dfrac{\varepsilon\alpha C^*}{\mu_{MU}} & -\left(\dfrac{\theta\alpha C^*}{\mu_{MU}} + \mu_{BI}\right) \end{pmatrix}. \tag{3.12}$$

The eigenvalues of $J(E_0)$ defined in (3.12) are given by $-(\alpha+\mu_C)$, $-\mu_{MU}$, $-\left(\dfrac{\varepsilon\alpha C^*}{\mu_{MU}} + \mu_{BI}\right)$, and the roots of the following quadratic equation:

$$\varsigma^2 + (\lambda C^* + \rho + \mu_{MI} + \eta C^* + \mu_{BE})\,\varsigma + (\lambda C^* + \rho + \mu_{MI})(\eta C^* + \mu_{BE})(1 - R_0) = 0.$$

The above implies that E_0 is locally asymptotically stable in Ω when $R_0 < 1$. From the equilibrium equation, we obtain

$$\begin{aligned} \varepsilon\nu B_E^* + \mu_{MU} &= \frac{\alpha C^*}{M_U^*}, \\ \lambda C^* + \rho + \mu_{MI} &= \frac{\varepsilon\nu B_E^* M_U^*}{M_I^*}, \\ \frac{\mu\sigma M_I^*}{K_m+\sigma M_I^*} - \theta M_U^* - \mu_{BI} &= -\frac{\varepsilon B_E^* M_U^*}{B_I^*}. \end{aligned} \tag{3.13}$$

Substituting (3.13) in (3.11), we obtain

$$J(E_1) = \begin{pmatrix} -(\alpha+\mu_C) & 0 & 0 & 0 & 0 \\ \alpha & -\dfrac{\alpha C^*}{M_U^*} & 0 & -\varepsilon\nu M_U^* & 0 \\ -\lambda M_I^* & \varepsilon\nu B_E^* & -\dfrac{\varepsilon\nu B_E^* M_U^*}{M_I^*} & \varepsilon\nu M_U^* & 0 \\ -\eta B_E^* & 0 & r\rho & -(\eta C^* + \mu_{BE}) & 0 \\ 0 & \varepsilon B_E^* - \theta B_I^* & \dfrac{\mu\sigma K_m B_I^*}{(K_m+\sigma M_I^*)^2} & \varepsilon M_U^* & -\dfrac{\varepsilon B_E^* M_U^*}{B_I^*} \end{pmatrix}. \tag{3.14}$$

The eigenvalues of $J(E_1)$ defined in (3.14) are $-(\alpha+\mu_C)$, $-\varepsilon B_E^* M_U^*/B_I^*$, and the roots of the following equation:

$$\zeta^3 + a_1\zeta^2 + a_2\zeta + a_3 = 0, \tag{3.15}$$

where

$$\begin{aligned}
a_1 &= \frac{\varepsilon\nu B_E^* M_U^*}{M_I^*} + \eta C^* + \mu_{BE} + \frac{\alpha C^*}{M_U^*},\\
a_2 &= \frac{\varepsilon\nu B_E^* M_U^*}{M_I^*}(\eta C^* + \mu_{BE}) - r\rho\varepsilon\nu M_U^* + \frac{\alpha C^*}{M_U^*}\left(\frac{\varepsilon\nu B_E^* M_U^*}{M_I^*} + \eta C^* + \mu_{BE}\right),\\
a_3 &= \frac{\alpha C^*}{M_U^*}\left[\frac{\varepsilon\nu B_E^* M_U^*}{M_I^*}(\eta C^* + \mu_{BE}) - r\rho\varepsilon\nu M_U^*\right] + \varepsilon\nu M_U^*\varepsilon\nu B_E^* r\rho.
\end{aligned}$$

Observe that

$$\frac{\varepsilon\nu B_E^* M_U^*}{M_I^*}(\eta C^* + \mu_{BE}) - r\rho\varepsilon\nu M_U^* = (\lambda C^* + \rho + \mu_{MI})(\eta C^* + \mu_{BE}) - r\rho\varepsilon\nu M_U^*.$$

Substituting M_U^* defined in (3.8) in the above equation, we obtain

$$\begin{aligned}
\frac{\varepsilon\nu B_E^* M_U^*}{M_I^*}(\eta C^* + \mu_{BE}) - r\rho\varepsilon\nu M_U^* &= (\lambda C^* + \rho + \mu_{MI})(\eta C^* + \mu_{BE}) - r\rho\varepsilon\nu\frac{\alpha C^*}{\mu_{MU} R_0}\\
&= (\lambda C^* + \rho + \mu_{MI})(\eta C^* + \mu_{BE})(1 - R_0/R_0)\\
&= 0.
\end{aligned}$$

Therefore, a_2 and a_3 are reduced to

$$\begin{aligned}
a_1 &= \frac{\varepsilon\nu B_E^* M_U^*}{M_I^*} + \eta C^* + \mu_{BE} + \frac{\alpha C^*}{M_U^*},\\
a_2 &= \frac{\alpha C^*}{M_U^*}\left(\frac{\varepsilon\nu B_E^* M_U^*}{M_I^*} + \eta C^* + \mu_{BE}\right),\\
a_3 &= \varepsilon\nu M_U^*\varepsilon\nu B_E^* r\rho.
\end{aligned} \tag{3.16}$$

Note that $a_i > 0$ for $i = 1, 2, 3$. In addition, from equilibrium equation (3.1), we verify

$$r\rho = (\eta C^* + \mu_{BE})\frac{B_E^*}{M_I^*},\ \varepsilon\nu M_U^* = (\lambda C^* + \rho + \mu_{MI})\frac{M_I^*}{B_E^*}.$$

Therefore,

$$\begin{aligned}
a_3 &= (\eta C^* + \mu_{BE})(\lambda C^* + \rho + \mu_{MI})\varepsilon\nu B_E^*\\
&= (\eta C^* + \mu_{BE})\frac{\varepsilon\nu B_E^* M_U^*}{M_I^*}\varepsilon\nu B_E^*.
\end{aligned}$$

Since $\alpha C^*/M_U^* > \varepsilon\nu B_E^*$, it is verified that $a_1 a_2 > a_3$. From the Routh-Hurwitz criterium [26], we conclude that the roots of Eq (3.15) have a negative real part, which implies that E_1 is locally asymptotically stable in Ω.

The following theorem summarizes the results of stability of the equilibria.

Teorem 3.2. *If $R_0 < 1$, then E_0 defined in (2) is locally asymptotically stable in Ω. If $R_0 > 1$ and $R_1 > 1$, E_0 is instable, and E_1 defined in (4) is locally asymptotically stable in Ω.*

4. Interpretation of bifurcation parameters

In this section, we will interpret and determine the biological meaning of the parameters R_0 and R_1, which govern the behavior of the solutions of system (2.2). For this purpose, we use the principles of immunology and epidemiology on the basic reproduction ratio presented by Nowak and May [27], and the parameter interpretation method used by Ibargüen and Esteva [28]. We begin by interpreting the parameters R_{MU}, R_{MI}, and R_{BE} defined by

$$\begin{aligned} R_{MU} &= \frac{\alpha C^*}{\mu_{MU}}, \\ R_{MI} &= \frac{\varepsilon\nu}{\lambda C^* + \rho + \mu_{MI}} = \frac{\mu_{MI}}{\lambda C^* + \rho + \mu_{MI}}\bar{R}_{MI}, \\ R_{BE} &= \frac{r\rho}{\eta C^* + \mu_{BE}} = \frac{\mu_{BE}}{\eta C^* + \mu_{BE}}\bar{R}_{BE}, \end{aligned}$$

where

$$\bar{R}_{MI} = \frac{\varepsilon\nu}{\mu_{MI}}, \; \bar{R}_{BE} = \frac{r\rho}{\mu_{BE}}.$$

Since α is the rate at which stem cells differentiate into macrophages and C^* is the equilibrium value of the stem cell population, $C(t)$, then αC^* is the rate at which stem cells differentiate into macrophages at their equilibrium level; that is, the number of uninfected macrophages generated from the stem cells will depend on the number of stem cells that reach an equilibrium state. In a similar way, λC^* is the apoptosis rate of infected macrophages at their equilibrium level, and ηC^* is the death rate of external bacteria due to the response of innate immune cells at their equilibrium level.

Now, R_{MU} is defined as the product of the rate of differentiation of stem cells into macrophages at their equilibrium, αC^*, by the average lifespan of uninfected macrophages, $1/\mu_{MU}$, and this parameter is interpreted as the average number of uninfected macrophages arising from stem cell differentiation. Similarly, $\bar{R}_{MI}$ is interpreted as the average number of infected macrophages infected generated by an external bacterium, and $\bar{R}_{BE}$ is interpreted as the average number of external bacteria generated by an external bacterium.

Note that

$$\frac{\mu_{MI}}{\lambda C^* + \rho + \mu_{MI}} = 1 - \frac{\lambda C^* + \rho}{\lambda C^* + \rho + \mu_{MI}}. \tag{4.1}$$

Since $\lambda C^* + \rho$ represents death by both apoptosis and necrosis, then

$$\frac{\lambda C^* + \rho}{\lambda C^* + \rho + \mu_{MI}}$$

represents the fraction of infected macrophages that die due to these types of cell death. In consequence, fraction defined in (4.1) determines the fraction of infected macrophages that survive both cell apoptosis and cell necrosis. Therefore, R_{MI} is interpreted as the number of infected macrophages generated by infected macrophages that survive both apoptosis and necrosis. Similarly, it follows that R_{BE} defines the fraction of external bacteria generated by external bacteria that survive the response of innate immune cells.

Let us observe that R_0 defined in (3.6) is rewritten as

$$R_0 = R_{BE}R_{MU}R_{MI}, \tag{4.2}$$

which represents the number of secondary infections generated by an external bacterium, when all innate cells are susceptible. Note that R_0 incorporates the infection dynamics of macrophages by external bacteria, while ignoring the role of internal bacteria in the infection process.

Before infection, we have $M_I = B_E = B_I = 0$, and innate immune cells and uninfected macrophages are at equilibrium $C = C^*$ and $M_U = \alpha C^*/\mu_{MU}$. If, at time $t = 0$, an individual is infected with an amount of external bacteria B_0, then the initial conditions are $x_0 = (C^*, \alpha C^*/\mu_{MU}, 0, B_0, 0)$. Whether or not the amount of bacteria can grow and establish an infection depends on the innate immune response. In our case, at the local level, if $R_0 < 1$, the Mtb will not spread. In other words, depending on the initial conditions, the infection will be cleared when $R_0 < 1$. This is based on the fact that each phagocytosed bacterium is being effectively eliminated by the macrophage response, indicating that an external bacterium will infect on average less than one macrophage. If $R_0 > 1$, then bacterial progression can occur (the phagocytosed external bacterium becomes an internal bacterium that begins its reproduction cycle inside the macrophage, which changes its state from uninfected to infected), sending signals to activate the adaptive immune response.

Bacterial persistence and activation of the specific immune response is determined by the values of R_0 and R_1. The parameter R_1 depends on both R_0 and all the parameters of the dynamics of internal bacteria. It incorporates the infection of macrophages by both external and internal bacteria. Since R_1 takes negative values, it cannot be interpreted as a basic reproductive radius. However, for $R_1 > 0$, we will interpret it as the number of infected macrophages produced by an infected macrophage (an external bacterium infects an uninfected macrophage, generating an infected macrophage and internal bacteria that reproduce inside the macrophage, until inducing necrosis of the same, which releases new bacteria into the environment).

5. Sensitivity analysis and numerical simulations

In the previous section, it was verified that the elimination of the infection depends on the basic radius of the offspring R_0 defined in (3.6), and that the bacterial progression and activation of the adaptive immune response depends on R_0 and R_1; in other words, if the primary infection is not controlled by the innate immune response, then to activate the adaptive immune response, in addition to the innate immune response, it is necessary to consider the level of pathogenicity of Mtb.

In this section, we will determine which parameters most influence the outcome of the infection and will present numerical simulations that verify the results of the qualitative analysis of the model (2.2). Table 1 contains a description of the parameters of system (2.2), together with a range of parameter values, obtained from the literature.

Table 2 summarizes the values of the thresholds R_0 and R_1, as well as the behavior of the equilibrium solutions E_0 and E_1 under different parameter sets.

Table 1. Parameters of model (2.2).

Parameter	Description	Parameter ranges	Units	References
Λ_C	Recruitment rate of C from stem cells	50 – 120	$cell/h$	[29]
α	Differentiation rate of C into M_U	0.02 – 0.06	h^{-1}	[31]
ε	Rate at which M_U phagocytose B_E	0.1 – 0.8	$(h \cdot cell)^{-1}$	[29]
ν	Rate at which engulfed B_E infects M_U	0.2 – 0.8	$cell/bact$	[29]
r	Average number of B_I released due to necrosis of M_I	1 – 50	$bact/cell$	[29]
η	Elimination rate of B_E by C	0.003 – 0.03	$(h \cdot cell)^{-1}$	[29]
λ	Apoptosis rate of M_I	0.008 – 0.19	$(h \cdot cell)^{-1}$	[29, 30]
ρ	Necrosis rate of infected macrophages	0.001 – 0.01	h^{-1}	[29]
μ_C	Natural death rate of C	0.0067 – 0.0083	h^{-1}	[29]
μ_{MU}	Natural death rate of M_U	0.0032 – 0.0051	h^{-1}	[31]
μ_{MI}	natural death rate of M_I	0.0101 – 0.0139	h^{-1}	[29]
μ_{BE}	Natural death rate of B_E	0.002 – 0.02	h^{-1}	[8]
μ_{BI}	Natural death rate of B_I	0.002 – 0.03	h^{-1}	[8]
μ	Maximum replication rate of B_I inside M_I	0.037 – 0.12	h^{-1}	[30, 32]
θ	Elimination rate of B_I by M_I	0.001 – 0.01	$(h \cdot cell)^{-1}$	[29]
K_m	Half-saturation constant	0.023 – 0.4227	$cell$	[30, 32]
σ	Proportionality constant	positive		assumption

Table 2. lbpr = lower bounds of the parameter ranges, ubpr = upper bounds of the parameter ranges, clubpr = combination of lower and upper bounds of the parameter ranges (upper (Λ_C, α, ε, μ_C, ν, r, μ, μ_{BI}, θ, K_m), lower (λ, ρ, η, σ, μ_{MU}, μ_{MI}, μ_{BE}).

Set of parameters	R_0	R_1	E_0	E_1
lbpr	2.78×10^{-4}	1.14×10^{6}	l.a.s	does not exist
ubpr	3.76×10^{-2}	4.56×10^{4}	l.a.s	does not exist
clupr	14.21	1.18×10^{5}	unstable	l.a.s

Let p be a parameter, and the normalized sensitivity index $\Upsilon_p^{R_0}$ is given by the following partial derivative:

$$\Upsilon_p^{R_i} = \frac{p}{R_i}\frac{\partial R_i}{\partial p}. \tag{5.1}$$

From (5.1), we verify $\Upsilon_\varepsilon^{R_0} = \Upsilon_\nu^{R_0} = \Upsilon_r^{R_0} = 1$, $\Upsilon_{\mu_{MU}}^{R_0} = -1$, and

$$\begin{aligned}
\Upsilon_{\Lambda_C}^{R_0} &= 1 - \left(\frac{\lambda C^*}{\lambda C^* + \rho + \mu_{MI}} + \frac{\eta C^*}{\eta C^* + \mu_{BE}}\right),\\
\Upsilon_{\alpha}^{R_0} &= 1 - \frac{\alpha}{\alpha + \mu_C}\left[1 - \left(\frac{\lambda C^*}{\lambda C^* + \rho + \mu_{MI}} + \frac{\eta C^*}{\eta C^* + \mu_{BE}}\right)\right],\\
\Upsilon_{\mu_C}^{R_0} &= -\frac{\mu_C}{\alpha + \mu_C}\left[1 - \left(\frac{\lambda C^*}{\lambda C^* + \rho + \mu_{MI}} + \frac{\eta C^*}{\eta C^* + \mu_{BE}}\right)\right],
\end{aligned}$$

$$\begin{aligned}
\Upsilon_{\lambda}^{R_0} &= -\frac{\lambda C^*}{\lambda C^* + \rho + \mu_{MI}}, \\
\Upsilon_{\rho}^{R_0} &= 1 - \frac{\rho}{\lambda C^* + \rho + \mu_{MI}}, \\
\Upsilon_{\mu_{MI}}^{R_0} &= -\frac{\mu_{MI}}{\lambda C^* + \mu_{MI}}, \\
\Upsilon_{\eta}^{R_0} &= -\frac{\eta C^*}{\eta C^* + \mu_{BE}}, \\
\Upsilon_{\mu_{BE}}^{R_0} &= -\frac{\mu_{BE}}{\eta C^* + \mu_{BE}}.
\end{aligned} \tag{5.2}$$

From (5.2), we observe that $\left\{\Upsilon_{\Lambda_C}^{R_0}, \Upsilon_{\mu_C}^{R_0}\right\} \in (-1, 1)$, $\Upsilon_{\alpha}^{R_0} \in (0, 2)$, $\Upsilon_{\rho}^{R_0} \in (0, 1)$, and $\left\{\Upsilon_{\lambda}^{R_0}, \Upsilon_{\mu_{MI}}^{R_0}, \Upsilon_{\eta}^{R_0}, \Upsilon_{\mu_{BE}}^{R_0}\right\} \in (-1, 0)$. These results reveal that parameters associated with innate immune cells show greater capacity to influence the outcome of infection. Figure 2 shows a graph in which infection with Mtb is cleared by the innate immune response. We observe that at the beginning, the population of external bacteria decreases, while the populations of infected macrophages and internal bacteria grow, indicating an infection process. After the rapid growth of the infected macrophage population, this population begins to decrease due to the different factors that lead to its elimination (apoptosis, necrosis, and natural death). The internal bacteria grow until they reach a peak. However, their population begins to decrease as the population of uninfected macrophages grows. In this case, the response of the macrophages was sufficient to eliminate the population of internal bacteria.

Figure 3 shows a graph in which bacterial progression is not eliminated by the innate immune response, and the conditions for the activation of the adaptive immune response are presented. As observed, shortly after the onset of infection, the population of extracellular bacteria decreases sharply, while simultaneously, the population of infected macrophages increases abruptly—indicating that the infection process has been effective. However, following this initial phase, the population of uninfected macrophages grows rapidly during the first 50 hours, a period in which it helps control the growth of the intracellular bacterial population. After reaching its peak, the infected macrophage population begins to decline in a damped oscillatory manner, a dynamic that is mirrored by the intracellular bacteria. Meanwhile, the innate immune cell population effectively controls the amplitude of the extracellular bacteria, nearly eliminating them. Nevertheless, these bacteria retain the ability to infect new macrophages, which are then regulated by immune cells and cell death mechanisms. Although the innate immune response shows the capacity to counteract bacterial progression, it ultimately proves insufficient to eradicate the infection entirely. As a result, the system tends toward a coexistence equilibrium involving all populations.

To complement the sensitivity analysis of the model parameters, we used the values from the simulation shown in Figure 3. The analysis was carried out on system (2.2), using the MATLAB odeSentivity function. The results revealed that the first equation of (2.2) is more sensitive to the parameters Λ_C and α, the second equation to Λ_C, α, ε, ν, r, η, λ, and ρ, the third to α and λ, the fourth to Λ_C, α, r, and λ, and the fifth to α, ε, r, λ, and ρ. From the above, it is observed that the most relevant parameter to reach the state of coexistence is α, followed by the parameters λ and Λ_C, parameters are associated with the response of the population of innate cells C. Finally, the graphs in Figure 4 show how an increase in α favors Mtb, while its reduction benefits the immune response of the host.

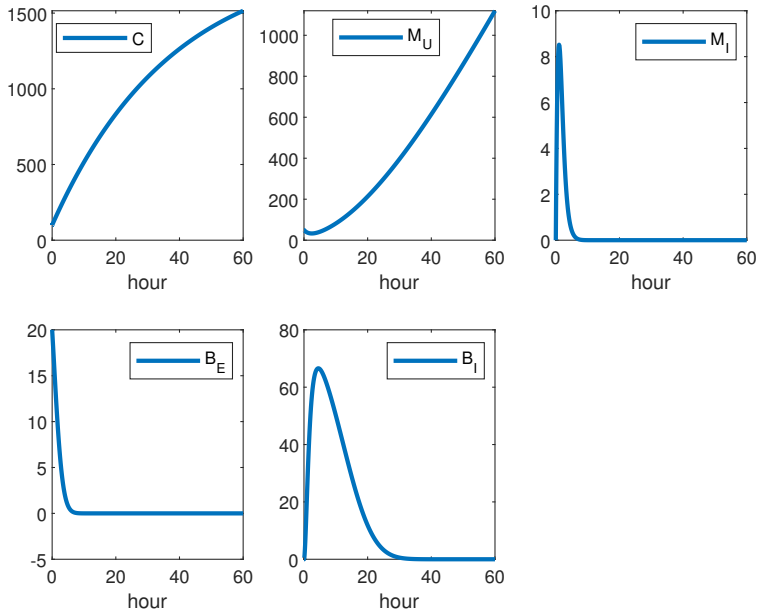

Figure 2. Temporal course of C, M_U, M_I, B_E, and B_I. These simulations were performed using the parameter set *lbpr* defined in Table 2, and the initial conditions $x_0 = (100, 50, 0, 20, 0)$.

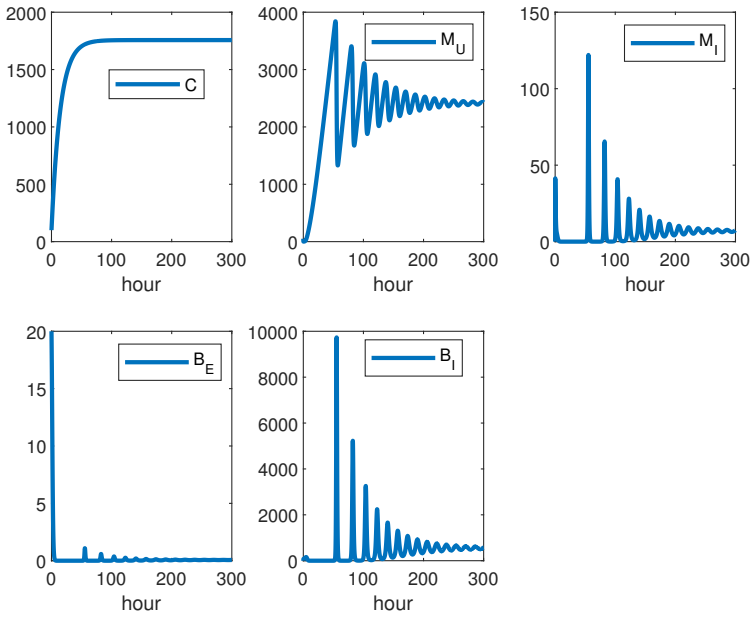

Figure 3. Temporal course of C, M_U, M_I, B_E, and B_I. These simulations were performed using the parameter set *clubpr* defined in Table 2, and the initial conditions $x_0 = (100, 50, 0, 20, 0)$.

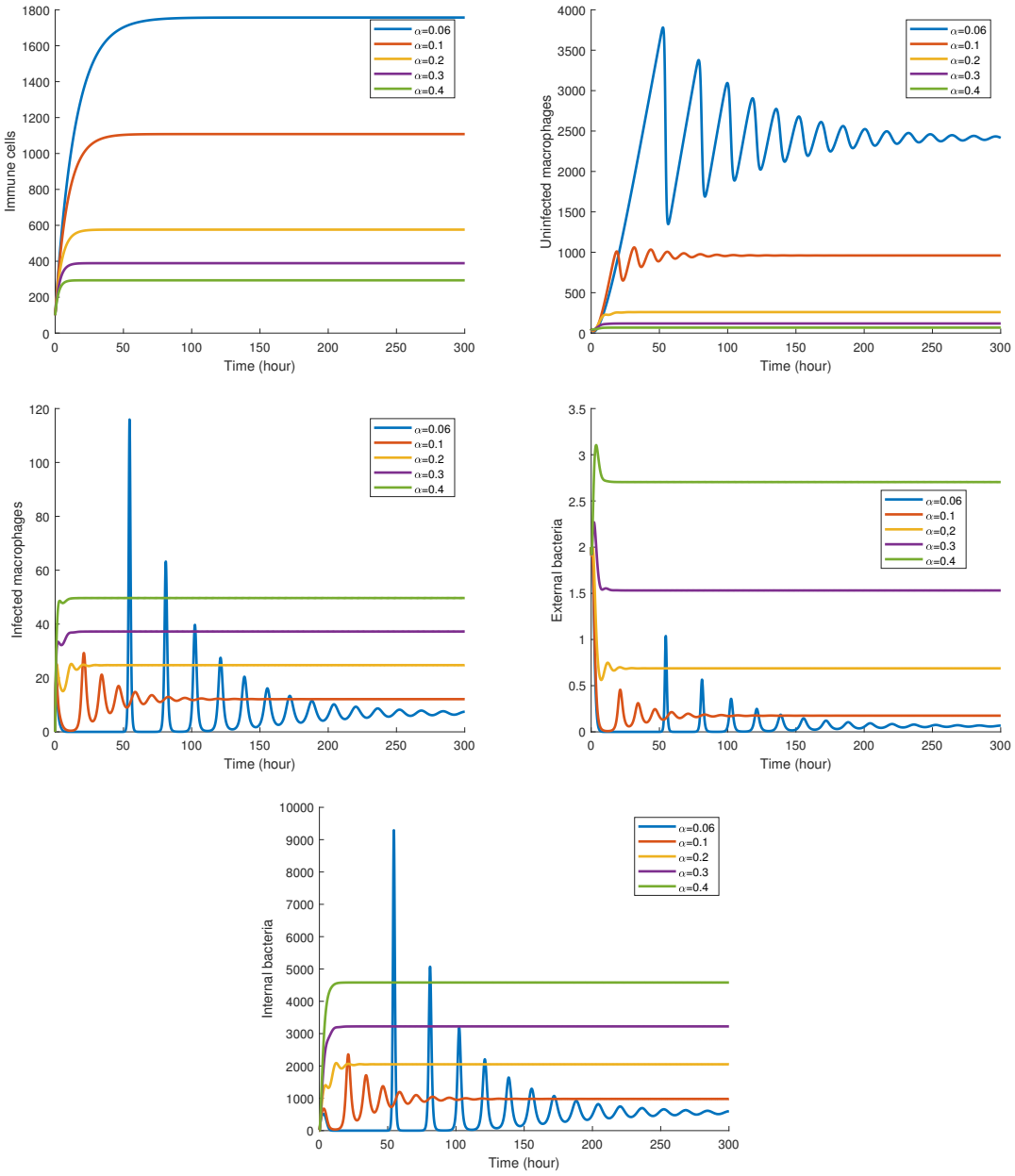

Figure 4. Temporal course of C, M_U, M_I, B_E, and B_I. These simulations were performed using the parameter set *clubpr* defined in Table 2, with α values of 0.06, 0.1, 0.2, 0.3, and 0.4, and the initial conditions $x_0 = (100, 50, 0, 20, 0)$.

6. Discussion

In this paper, we formulated a dynamical system on the innate immune response to Mtb, in order to evaluate the effectiveness of macrophages and other innate cells in controlling primary infection with Mtb. In these interaction dynamics, it is assumed that the innate response of macrophages and other innate cells is governed by the law of mass action. The results predict, in terms of the basic radius of the offspring R_0 and the parameter that includes the response against the total bacteria population, R_1, when the bacteria are cleared due to innate immune response or the infection progresses generating appropriate conditions to activate the adaptive immune response.

R_0 has the structure of a multiplicative basic reproductive number. In fact, it is the product of three basic numbers: the fraction of external bacteria generated by external bacteria that survive the response of innate immune cells, R_{BE}, the average number of macrophages arising from stem cell differentiation, R_{MU}, and the number of infected macrophages generated by infected macrophages that survive both apoptosis and necrosis, R_{MI}. Qualitative analysis revealed that if $R_0 < 1$, then the solutions of (2.2) locally approach the infection-free equilibrium E_0. That is, bacterial progression will tend to be controlled, and there will be no need to activate the innate immune response. A few decades ago, this result had no experimental support, but new insights are supporting it [6, 33].

At the local level, bacterial progression does not necessarily persist when $R_0 > 1$, and the results suggest two scenarios: a) an outbreak of infection occurs at the beginning, which is subsequently eliminated or controlled by the innate immune response ($R_0 > 1$ and $0 < R_1 \leq 1$), or b) an outbreak occurs at the beginning that generates bacterial persistence and the appropriate conditions to activate the adaptive immune response ($R_0 > 1$ and $R_1 > 1$).

However, the results suggest that although they work in the front line of the innate immune response, the primary protective response against Mtb needs the synergy and contribution of both macrophages and other innate cells. Furthermore, sensitivity analysis revealed that the parameters that most influenced the outcome of the infection were those associated with the population of innate cells, C.

7. Conclusions

The immune response against TB has always focused on understanding the adaptive immune response, leaving aside the innate immune response. In this regard, new insights have shown that the first immune response is very important, that not only do macrophages play a fundamental role, but that there are also other innate cells that are key to fighting the infection.

Currently, progress has been made in relation to the innate cells that participate in the response against TB; however, the role they play is still lacking in understanding. In this work, it was demonstrated that the infection-free equilibrium, E_0, is locally asymptotically stable when $R_0 < 1$. This suggests that if the immunological condition of an infected individual is strong enough to prevent external bacteria from infecting the macrophage population; that is, if the external bacteria phagocytosed by macrophages are eliminated or their capacity to reproduce is limited, then the innate immune response will be able to eliminate or control bacterial progression.

On the other hand, if $R_0 > 1$: that is, if the external bacteria have the capacity to infect macrophages, the results suggest several scenarios. a) Bacterial progression will not necessarily lead to bacterial

persistence. There is the possibility that an initial outbreak may occur, but in the end the bacterial progeny will be controlled by the innate immune system. b) Bacterial progression cannot be controlled and the appropriate conditions for the activation of the adaptive immune response are generated.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare there is no conflict of interest.

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