A Model Describing the Response of the Immune System to *Mycobacterium tuberculosis*

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ABSTRACT

We present a mathematical model to describe the dynamics of the immune system in the presence of the causative agent of tuberculosis, *Mycobacterium tuberculosis*. We take into consideration the relations between the bacteria, T lamphocytes, and macrophages. We compute the basic reproductive number to determine under which conditions we get certain disease states: no infection, latency, and infection. The behavior depicted by our model, under certain parameters, demonstrates the dynamics of these three conditions of the disease. We consider a treatment and analyze its effect on the dynamics of the system.

1 Introduction

During the 1800s, tuberculosis was an epidemic disease throughout the world. Due to improvements in living conditions and advances in medicine, the incidence of tuberculosis began to decline in the 1900s. However, it has remained a major cause of death in developing countries. It is transmitted through coughs and sneezes by a person with infectious (active) tuberculosis. Healthy persons who are infected have a high probability of being asymptomatic. There is a 10% risk of developing active tuberculosis after being infected [Hopewell 1994]. When tuberculosis is latent, it is incapable of being transmitted and does not cause any symptoms [Miller 1993].

Currently the number of cases of tuberculosis again is on the rise. Approximately one third of the global population is infected by *Mycobacterium tuberculosis* [Sudre *et al.* 1992], the causative agent of the disease. This makes tuberculosis one of the most common infectious diseases in the world. Some of the factors that have caused this increase of the disease are: immigration, overcrowded living conditions, substance abuse, and AIDS. Newly evolved strains that are resistant to one or more drugs used in treatment have developed with this new resurgence of tuberculosis.

An increase in awareness has motivated basic research on the pathogenesis of the bacteria and the mechanisms of the immune response. Our research is based on the microbiological perspective of tuberculosis and the immune system. The focus is on the immune system-pathogen interaction. Work using this approach has been done with Chagas' disease [Velasco-Hernández and Pérez-Chavela 1992] and the HIV virus.

In tuberculosis, the interaction among the causative agent, the macrophages, and the T cell (CD4/CD8) populations establishes the state of the disease. The interaction between the bacteria and the immune system can be viewed as the combination of two ecological processes: predator-prey and pathogen-host interaction. Using this blended model, we analyze the potential outcomes resulting from human exposure to *Mycobacterium tuberculosis*. Three outcomes will be examined: no infection, a latent state of infection, and an infectious (active) state. The present paper seeks to model the dynamics between the *Mycobacterium tuberculosis* and the cells of the immune system by considering five separate populations: *Mycobacterium tuberculosis*, empty macrophages, inactivated macrophages, activated macrophages, and T cells.

We seek to determine which initial states and which parameters lead to different outcomes in the health of the infected individual. From these findings we will have a better understanding of the immune system and its response to *Mycobacterium tuberculosis*. This may enable scientists to foresee and prevent the death of an infected individual.

2 Mathematical Model

A realistic model of the interactions between the immune system and *Mycobacterium tuberculosis* is required to elucidate the dynamics of these interactions. A notable limitation in the construction of this model has been the lack of understanding the mechanisms involving the immune response to *Mycobacterium tuberculosis*. To account for these limitations it is necessary to make some assumptions about the process and incorporate them into our model. There is still an ongoing debate as to the importance of the role of the humoral response, but in order to simplify the model we have assumed that it is negligible and have concentrated exclusively on the cell-mediated response.

The cell-mediated immune response includes the action of macrophages, or phagocytic cells able to digest foreign material, and T cells which facilitate the activation of the response by secreting growth and cell-activating factors. The model discussed here includes effects of $CD4^+$ and $CD8^+$ T cells. We do not distinguish between these two subpopulations. More explicitly, we have taken the liberty to consider their total effects as additive. Therefore we focused on a broader concept of a T cell which combines the outcomes of both these subpopulations.

A very important note to consider is that our model presumes infection and concentrates on the possible outcomes of this infection. We consider infection only in the primary infection site. We do not consider spread of the bacteria via travel of the alveolar macrophages into other parts of the body nor do we consider systemic infection. We have considered three general outcomes which are summarized in Figure 1. All outcomes presume engulfment of bacilli by the alveolar macrophage. Once in the macrophage, the bacilli can restrain their growth and remain unnnoticed for years. The length of time which these bacilli can remain unnoticed inside macrophages depends on the individual. Genetic patterns have been observed with respect to the

length of this latent state (Rossman & Macgregor 1995). If the bacilli replicate once inside the macrophage, the stress of this activity will lead to an immune response involving the T cells. From the latent state we can have reactivation of bacterial replication which will lead to a similar response. The mechanisms which activate this replication in latent-state bacilli remain unclear. Once an immune response is mounted we have two possible outcomes: defeat of the bacilli due to their destruction and elimination, and uncontrolled infection whereby the immune response was not strong enough to eliminate the pathogen, leading to symptomatic tuberculosis. Thus we consider the outcomes of infection as latency, infection progression, or infection elimination.

2.1 Macrophage growth and infection

In order to consider the relation of the macrophages to the system we have to consider the roles they play in the immune response mounted against the bacteria. We consider three states of the cell. The first is the free state before its encounter with a bacilli (M). In this state it simply remains prepared for an encounter with a foreign antigen. The next state is the inactive state from chance encounters with a tuberculosis bacilli (M^*). In the inactive state it now contains the bacilli within its cytoplasm (i.e., it is now full) yet remains inactivated. The third state consists of the activated full macrophage (M^{**}). Activation occurs from chance encounters of a T cell which, after recognizing it, begins to mount an attack partly by activating the macrophage. The actual process of activation is also unclear, although there are some hypotheses, including the belief that when the T cell activates the macrophage it enables it to produce nitrogenous compounds which the bacilli cannot resist. As a model for these three states we suggest the following:

$$dM/dt = \beta - \delta M - \epsilon MP, \quad (1)$$

$$dM^*/dt = \epsilon MP - \alpha TM^* - (\delta + g)M^*, \quad (2)$$

$$dM^{**}/dt = \alpha TM^* - \delta M^{**}, \quad (3)$$

where β represents the birth rate of macrophages as seen in the bone marrow of a healthy adult; δ the natural cell death rate; ϵ the engulfing rate of a macrophage with respect to a bacillus; α the activation rate of a full macrophage with respect to its encounter with a T cell; and g the rate of

bursting of a macrophage as a result of the unbounded proliferation of bacilli inside its cytoplasm.

We have left out the possibility of a varying birth rate, although taking this possibility into account would make our model more realistic, since there is an increase in macrophages when a full one meets up with a T cell.

2.2 T cell proliferation

Immune response depends on chance encounters of T cells with M^* macrophages. The T cell recognizes the M^* macrophage and begins mounting an attack that not only activates the macrophage but also allows for the secretion of substances such as INFγ (which kills free bacteria as well as destroys surrounding tissues). The T cells also self-replicate in the process. Thus we consider the following equation to model the dynamics of the T cells:

$$dT/dt = \Lambda + rTM^* - \delta_T T. \tag{4}$$

where Λ is the birth rate for the formation of the T lymphocyte in the bone marrow of a healthy adult; δ_T is the natural cell death rate of the T cell; and r is the rate of replication of the T cell upon encountering a full macrophage. We have assumed that the birth rate is constant but we are aware that it should be represented as a function of T.

2.3 *M. tuberculosis* growth in an infected individual

The causative agent of tuberculosis is transmitted via the inhalation of infectious droplets emitted during an infected person's coughing, sneezing, or spitting. The contraction of the disease by a susceptible guinea pig or rabbit depends on the inhalation of droplets limited to the size of 1 to 3 bacilli in order to facilitate their engulfment by macrophages. Equivalent data is not found on humans so we have assumed a similar pattern of dependence in modeling the immune response for humans. As a model we propose:

$$dP/dt = bP - \delta_P P - \epsilon MP + (\delta N + gL)M^*, \tag{5}$$

where P is the number of bacilli as would be measured in the blood; δ_P the natural cell death rate; N the number of bacilli inside a macrophage when it dies a natural cell death; and L the number of bacilli required in order to burst a macrophage.

3 Analysis and Simulations

3.1 Analysis

Our model consists of the following set of differential equations:

$$\begin{aligned} dM/dt &= \beta - \delta M - \epsilon MP && (6)\\ dM^*/dt &= \epsilon MP - \alpha TM^* - (\delta + g)M^* && (7)\\ dM^{**}/dt &= \alpha TM^* - \delta M^{**} && (8)\\ dT/dt &= \Lambda + rTM^* - \delta_T T && (9)\\ dP/dt &= bP - \delta_P P - \epsilon MP + (\delta N + gL)M^*. && (10) \end{aligned}$$

To begin the analysis of the system we compute the steady states for (6) – (10). For the disease-free equilibrium we take $P = 0$, $M^* = 0$, and $M^{**} = 0$, since in the absence of bacteria we would have no engulfing, hence no M^* nor M^{**} cells. From (1) and (4) we have

$$0 = \beta - \delta M \qquad \text{and} \qquad 0 = \Lambda - \delta_T T$$

so

$$E_0 = (M_0, M_0^*, M_0^{**}, T_0, P_0) = (\beta/\delta, 0, 0, \Lambda/\delta_T, 0).$$

The Jacobian matrix of the system at E_0 is

$$J_{E_0} = \begin{pmatrix} -\delta & 0 & 0 & 0 & -t\frac{\beta}{\delta} \\ 0 & -\left(\delta + g + \alpha\frac{\Lambda}{\delta_r}\right) & 0 & 0 & t\frac{\beta}{\delta} \\ 0 & \alpha\frac{\Lambda}{\delta_r} & -\delta & 0 & 0 \\ 0 & 0 & 0 & -\delta & 0 \\ 0 & \delta N + gL & 0 & 0 & b - \delta_p - \epsilon\frac{\beta}{\delta} \end{pmatrix}.$$

Let

$$C = \begin{pmatrix} -\left(\delta + g + a\frac{\Lambda}{\delta_r}\right) & t\frac{\beta}{\delta} \\ \delta N + gL & b - \delta_p - e\frac{\beta}{\delta} \end{pmatrix}.$$

For the stability of E_0, we can see that the real part of all eigenvalues of the matrix J_{E_0} is negative if and only if both

$$det(C) = (\alpha\Lambda/\delta_T + \delta + g)(\epsilon\beta/\delta + \delta_P - b) - (\delta N + gL)(\epsilon\beta/\delta) > 0,$$

and

$$tr(C) = -(\alpha\Lambda/\delta_T + \delta + g) - (\epsilon\beta/\delta + \delta_P(b) < 0.$$

The condition in the determinant is equivalent to

$$\frac{(\epsilon\beta/\delta)(\delta N + gL)}{(\epsilon\beta/\delta + \delta_p - b)(\alpha\Lambda/\delta_T + \delta + g)} < 1.$$

We define the basic reproductive number as

$$\frac{(\epsilon\beta/\delta)(\delta N + gL)}{(\epsilon\beta/\delta + \delta_p - b)(\alpha\Lambda/\delta_T + \delta + g)}.$$

This parameter relates the average number of engulfings per lifetime of M $(\epsilon\beta/\delta)$ per "true" lifetime of bacteria $(\epsilon\beta/\delta + \delta_p - b)$ with the average number of released bacteria $(\delta N + gL)$ per "true" lifetime of M^* cells $(\alpha\Lambda/\delta_T + \delta + g)$. R_0 reflects the interplay of epidemiological, predator-prey, and population growth factors in our model. It relates epidemiological factors for the $M \rightarrow M^* \rightarrow M^{**}$ dynamics, predator-prey interactions between the M and P population, and the population dynamics of P.

For R_0 to make sense we should have $\epsilon\beta/\delta + \delta_P - b > 0$. If we consider the case when $\epsilon\beta/\delta + \delta_P - b < 0$, then bacteria will increase exponentially. To see why this happens, from (1) we can see that $M < \beta/\delta$. From (5) we have

$$dP/dt \geq (b - \delta_P - \epsilon\beta/\delta)P;$$

thus

$$P(t) \geq P(0)e^{(b-\delta_P-\epsilon\beta/\delta)t} \rightarrow \infty \text{ as } t \rightarrow \infty.$$

To determine endemic equilibria, we set equations (1) – (5) equal to zero. From (4) and (5) ,

$$T = \Lambda\delta_T - rM^* \quad \text{for} \quad M^* < \delta_T/r \qquad \text{and} \qquad P = \frac{(\delta N + gL)M^P*}{\delta_p + \epsilon M - b}.$$

Substituting these equations in (1) and (2), we have

$$0 = \beta - \delta M - \epsilon M \frac{(\delta N + gL)M^*}{\delta_p + \epsilon M - b}$$

and

$$0 = \epsilon M \frac{(\delta N + gL)M^*}{\delta_p + \epsilon M - b} - \alpha \frac{\Lambda}{\delta_T - rM^*} M^* - (\delta + g)M^*. \qquad (*)$$

Adding these two equations and solving for M gives us

$$M = \frac{1}{\delta}\left[\beta - \frac{\alpha\Lambda M^*}{\delta_T - rM^*} - (\delta + g)M^*\right].$$

Let $x = M^*$, then let $g_1(x) = \delta_T - rx$, $g_2(x) = [\beta - \delta + g)x]g_1(x) - \alpha\Lambda x$. Then M can be expressed as

$$M = \frac{g_2(x)}{\delta g_1(x)} \quad \text{with} \quad x = M^*.$$

Substituting M in the second equation from (*) and considering $M^* > 0$ we define

$$F(x) = \frac{\epsilon(\delta N + gL)g_2(x)}{(\delta_p - b)\delta g_1(x) + \epsilon g_2(x)} - (\delta + g) = 0.$$

Take

$$e_1(x) = \frac{\epsilon(\delta N + gL)g_2(x)}{(\delta_p - b)\delta g_1(x) + \epsilon g_2(x)}, \quad e_2(x) = \frac{\alpha\Lambda}{g_1(x)} + (\delta + g).$$

Solving for x $(= M^*)$ would be finding x such that these two curves intersect: $e_1(x) - e_2(x) = 0$.

We show the existence of such an x, hence the existence of endemic equilibria. We restrict the analysis to the interval $[0, \delta_T/r)$. Note that $F(0) = e_2(0)(R_0 - 1)$. For $R_0 > 1$ we have $F(0) > 0$. Now consider $x* = \delta_T/r$. Note that

$$\lim_{x \to x*} e_1(x) = \delta N + gL, \quad \text{and} \quad \lim_{x \to x*} e_2(x) = \infty.$$

Then

$$\lim_{x \to x*} F(x) = -\infty.$$

Since $F(0) > 0$ and for some h, $F(\delta_T/r - h) < 0$, then $F(c) = 0$ for some $c \in (0, \delta_T/r)$. This shows the existence of an endemic equilibrium. We now show that for $\delta_p \geq b$ the endemic equilibrium is unique. Computing $F'(x)$,

$$F'(x) = \delta\epsilon(b - \delta_p)(\delta N + gL)[(\delta + g)g_1^2 + \alpha\Lambda g_1 + r\alpha\Lambda x] - \frac{\alpha\Lambda r}{g_1^2},$$

we can see that for $\delta_P \geq b$, $F'(x)$ is strictly negative. This shows that there is only one $c \in (0, \delta_T/r)$ such that $F(c) = 0$, when $R_0 > 1$.

3.2 Simulations

We complete our analysis through computer simulations. In the previous section, we determined analytically the conditions for stability of the disease-free equilibrium, the existence of endemic equilibria for $R_0 > 1$, and the uniqueness of an endemic equilibrium for the case where $\delta_P \geq b$, with $R_0 > 1$.

Through the simulations we corroborated our analytical results and extended them. The main purpose of the simulations was to find the three possible stages of tuberculosis: active, latent, and no TB. We identified the active stage with an exponential growth of the bacteria, the latent stage with an endemic equilibria, and the no-TB stage with the disappearance of bacteria.

While doing the simulations, we considered the cases where $R_0 < 1$ and $R_0 > 1$. This was done because of the lack of information on most of the parameters. We define

$$R_1 = \frac{\epsilon\beta/\delta}{\epsilon\beta/\delta + \delta_p - b} \quad \text{and} \quad R_2 = \frac{\delta N + gL}{\alpha\Lambda/\delta_T + \delta + g}.$$

For each of the cases, we considered three sub-cases, each a different combination of values for R_1 and R_2. For $R_0 < 1$ we considered: 1) $R_1 < 1$, $R_2 < 1$; 2) $R_1 > 1$, $R_2 < 1$; 3) $R_1 < 1$, $R_2 > 1$. For $R_0 > 1$ we considered the cases: 1) $R_1 > 1$, $R_2 > 1$; 2) $R_1 > 1$, $R_2 < 1$; 3) $R_1 < 1$, $R_2 > 1$. In each of these cases we paid most attention to the behavior of $P(t)$ (bacteria) and $M(t)$ (macrophages).

We obtained no TB ($P(t) \to 0, \quad M(t) \to \beta/\delta$) in the cases where $R_0 < 1$ and $R_1 < 1$. This can be interpreted as follows: $R_1 < 1$ is true only if $\delta_P > b$. Since bacteria is dying at a higher rate than their birth we would expect a settled growth of bacteria. With $R_0 < 1$ this behavior settles to the disease-free equilibrium.

Our model showed latency ($P(t) \to k_1$, $M(t) \to k_2$) in the case where $R_0 > 1$, with $R_1 < 1$ and $R_2 > 1$. $R_1 < 1$ means $\delta_P > b$, and $R_2 > 1$ means that there is a higher "release" rate of bacteria with respect to the removal of M^* cells through activation. A latent stage is expected with high release rate and high death rate for bacteria since it is plausible to get a "balanced" system.

We found active TB ($P(t) \to \infty$, $M(t) \to 0$) in the case where $R_0 > 1$, $R_1 > 1$ and $R_2 > 1$. This can be interpreted as the consequence of $b > \delta_P$ ($R_1 > 1$) and a high release rate ($R_2 > 1$).

We also obtained interesting results for the cases where $R_1 > 1$ and $R_2 < 1$, both with $R_0 < 1$ and $R_0 > 1$. For some initial conditions, as the ratio R_1/R_2 increased we could observe a transition from a disease-free state to an active stage of exponential growth for $P(t)$. This was obtained for $R_0 > 1$ and $R_0 < 1$. The transition was sensitive to initial conditions. We do not give a biological interpretation because of the complex behavior. See Appendix for graphs.

3.3 Treatment

It is interesting to note the possible effect of treatment on the dynamics of the system. We consider a drug with an intracellular and an extracellular effect. Equations (2) and (5) would be modified in the following way:

$$dM^*/dt = \epsilon MP - \alpha TM^* - (\delta + g)M^* - \phi M^*,$$

and

$$dP/dt = (b - \delta_P)P - \epsilon MP + (\delta N + gL)M^* - \phi P.$$

The corresponding basic reproductive number is

$$R_0(\phi) = \frac{(\epsilon\beta/\delta)(\delta N + gL)}{(\epsilon\beta/\delta + \delta_P - b + \phi)(\alpha\Lambda/\delta_T + \delta + g)\phi)}.$$

From $R_0(\phi)$ we can note that the effect of treatment is an expansion of the domain of parameters that stay within the condition$R_0 < 1$, with $R_1 < 1$ and $R_2 < 1$.

4 Discussion

Our paper we proposes a system of differential equations to describe what happens when tuberculosis is in an infected individual. We found in our solution analysis the three possible results of TB after it attacks the body: latent or inactive TB, active TB, or a full recovery from the infection.

Our first important step in the analysis of our model was obtaining R_0, the basic reproductive number, which gave us the conditions of the three possible outcomes of TB when it attacks the individual. We also were able to find the stability condition in the disease-free state. In addition, we were able to prove the existence of an endemic state when $R_0 > 1$. In particular, if $\delta_b > b$ then we are guaranteed uniqueness of this endemic equilibrium with $R_0 > 1$.

In our analysis, we saw the importance of the engulfing mechanism. The macrophages served as a "reservoir" for the *Mycobacterium tuberculosis*. Either the bacteria are released into the immune system by explosion or the macrophages annihilate the bacteria. Through computer simulations, we were able to identify the important factors of the system that gave us different outcomes. These factors are: the birth of the bacteria, the death of the bacteria, the engulfment rate of the bacteria by the macrophages, the release of the bacteria by the macrophages, and the activation rate of the macrophages by the T-cells. Another important result was the interesting outcomes during the latent state of the disease. Latency was either permanent, temporary, or the person made a full recovery from the disease. From our system of differential equations, we found the three outcomes that we wanted to find, depending on the value of R_0 , R_1 ,and R_2.

However, our model did behave strangely; some of the analytical interpretations did not coincide with the computer analysis. There are special conditions in the model, such as a "gray area" where a slight change in the value of certain parameters changes the state of tuberculosis. A plausible explanation for the unusual behavior in the model is that many of the parameters in the model have not been found. For example, the engulfing rate of the bacteria is questionable. Also, we do not know the duration of the hibernation period of the bacteria in the macrophage. The lack of biological parameters limited our interpretation of our mathematical model.

The immunological model was further extended to include an intracellular and an extracellular treatment. This new parameter would be subtracted from the P and M^* equation. This would affect the R_0 because the new term would appear in the denominator of the basic reproductive number. Time did not permit us to do a complete analysis but from our interpretation of the model, we see that the likelihood of proper treatment raised the chances to a full recovery.

A possible area for further research is to extend the model to include another factor that is causing a weak immune system, such as HIV. Anyone infected with HIV is more likely to die of tuberculosis because HIV weakens the system, often allowing the tuberculosis to take over the immune system. Studies have shown that certain groups are more likely to become infected with tuberculosis than others, such as substance abusers, smokers, and the poor. We could accommodate the model to become specific to high-risk groups. We may be able to find similar patterns between each of these groups and be able to easily identify others who will fall in the defined high-risk group. Can a target treatment be designed for these high-risk groups? What happens if we consider resistant strains? We hope this project will lead others to study these important questions concerning the disease.

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6 Appendix

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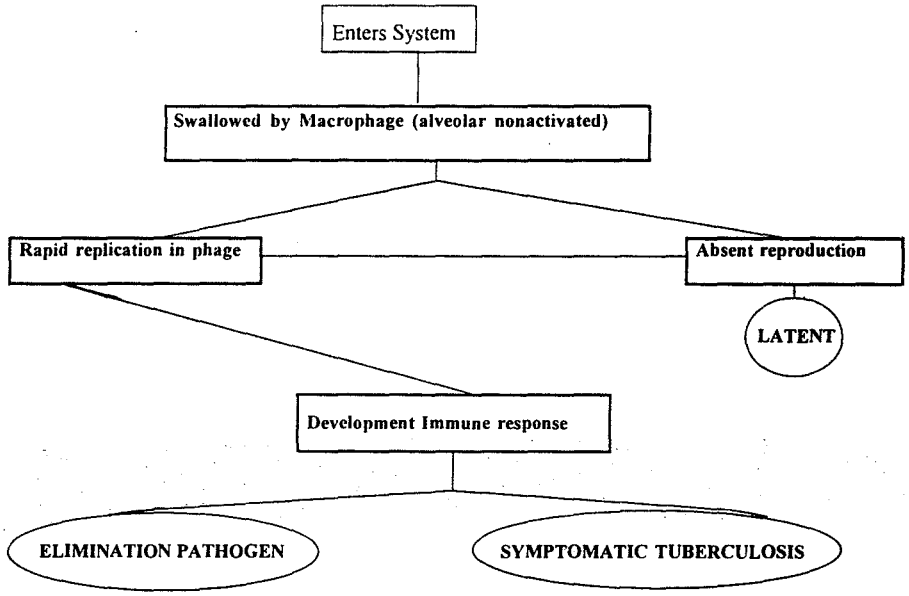
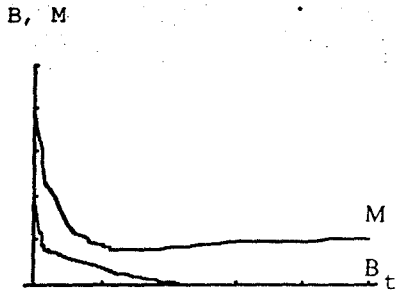
6. Appendix

Figure 1
Visible dynamics of Tuberculosis and the Immune System

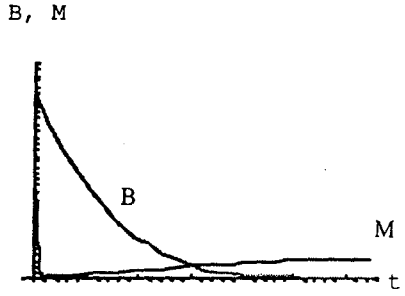


$R_0 < 1$:

Figure 2



$R_1 < 1, R_2 < 1$



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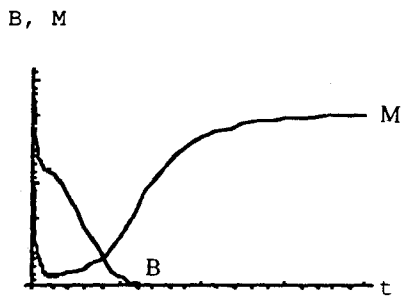
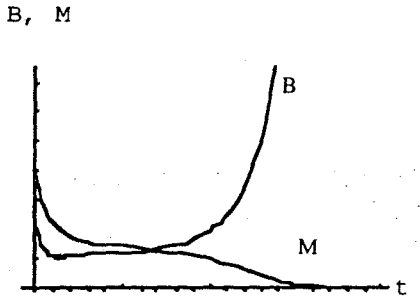


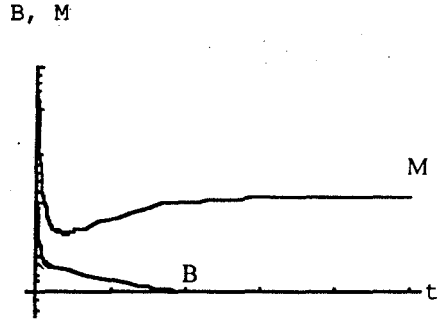
$R_1 > 1, R_2 < 1$



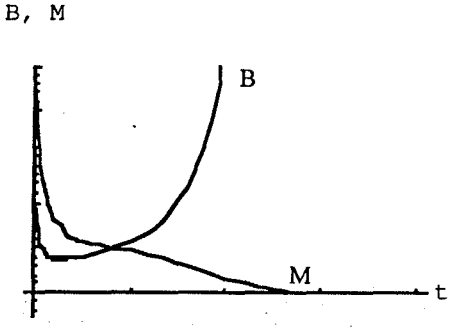
$R_1 > 1, R_2 < 1$

$R_0 > 1$

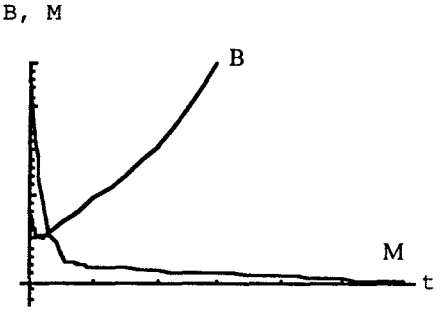
Figure 3



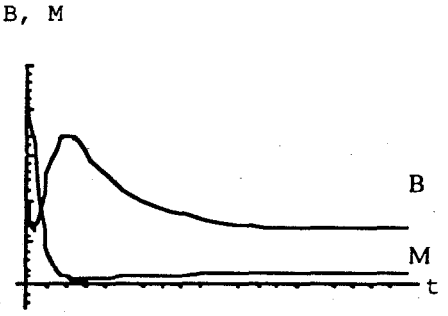
$R_1 > 1, R_2 < 1$



$R_1 > 1, R_2 < 1$

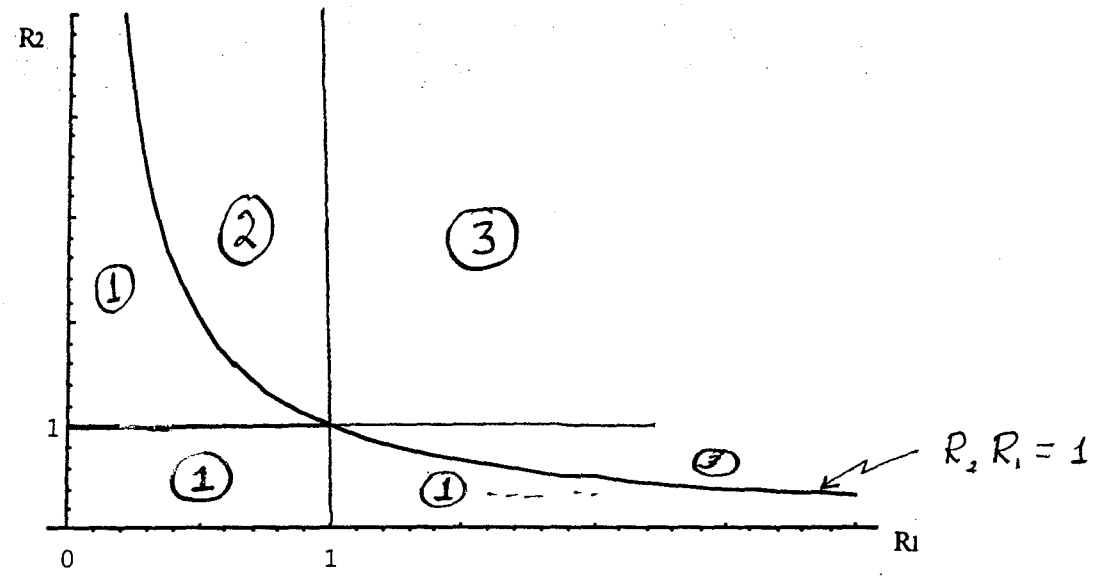


$R_1 > 1, R_2 > 1$



$R_1 < 1, R_2 > 1$

Figure 4 A Model Describing the Immune System to M. tuberculosis.



Outcomes after exposure: 1 - No TB, 2 - Latent TB, 3 - Active TB, depending on the values of parameters R_1 and R_2. The region under the curve is when $R_0 < 1$; over the curve we have $R_0 > 1$.