A Mathematical Model for Macrophage, T Cell, and Mycobacterium Tuberculosis Interactions

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Abstract

We present a mathematical model based on a system of nonlinear ordinary differential equations to describe the dynamics of the macrophages and T lymphocytes in the presence of a causative agent of tuberculosis, Mycobacterium tuberculosis. This model takes into consideration the relations among six different populations inside the lung of an infected individual. These populations are bacteria, non-activated and activated T lymphocytes, non-infected macrophages, non-activated infected macrophages, and activated macrophages. We study and characterize the stability of an infection's free state which represents an equilibrium point of the governing system of equations. In addition, we show the existence of a family of infectious steady states for values of the parameters for which the infection's free state becomes unstable. We present computer simulations based on some known parameter values from the literature. Also, we show by computer simulations that our model equations can exhibit Hopf bifurcation and construct examples of stable non-trivial steady states and periodic solutions.

Key words: Tuberculosis, population interaction model, bifurcation analysis.

1 Introduction

Tuberculosis (TB) is an infective disease caused mainly by a bacterium called *Mycobactirium Tuberculosis*. An infected individual transmits TB through coughs and sneezes. Once the person gets the TB bacteria, the immune system response could destroy or inhibit the spread of the bacteria. If the bacteria are inhibited instead of destroyed, TB could be latent for a period until the immune system becomes weak. This will raise the number of TB bacteria resulting in an active or infectious TB, see [1].

The number of TB cases has drastically increased in recent years. The reasons for that increase in TB cases has been attributed to: the human immunodeficiency virus (HIV) that debilitates the immune system of the person infected with it and the multi-drug resistance developed when the treatment of a TB patient is interrupted or inadequate [2], [3], [4]. Castillo-Chávez and Feng in [5], studied the dynamic of resistant TB using a basic transmission model. We refer to that article along with its extensive references for details about the epidemic aspects of TB. In view of the increase in the number of TB cases, it is important to understand the interaction of the TB bacteria with the immune system.

In this article, we approach the interaction of the TB bacteria with the immune system by a mathematical model. The model presented here makes use of predator-prey processes and kinetic reactions. The immune response to the TB bacteria includes the action of macrophages and T cells. The macro-

phages ingest bacteria and are able to destroy or inhibit them. Whereas, T cells secrete a substance that activate and attract macrophages. For a detailed discussion see [6], [7].

By using this model, we analyze two basic outcomes resulting from the human exposure to the TB bacteria: the infection's free state and the infectious state. We consider six populations as the most significant in the above states.

Mathematical models for the interaction of the immune system with the HIV virus have been given among others by Perelson [8] and Kirschner [9]. The interaction of the T cell with antigen presenting cells has been modeled among others by Fishman and Perelson [10], where dentritic cells and macrophages were considered as presenting cells.

In Section 2 of the paper, we describe all the basic assumptions in our model and present the mathematical equations. In Section 3 we study the existence and stability of equilibrium points for the proposed model. In particular, we show that an equilibrium point representing an *infection's free state* exists for all permissible values of the parameters in the problem and find conditions on the parameters that guarantee the stability of this point. Moreover, we prove the existence of a surface of *infectious steady state* points bifurcating at the point at which the infection's free state looses stability. In Section 4 we present some numerical simulations. We use some parameter values from the available literature together with the stability criteria from Section 3 to compute an infectious equilibrium point. Furthermore, we show

that our model exhibits Hopf bifurcation for certain values of the parameters and construct a periodic solution of the system.

2 The Mathematical Model

The progression of the TB infection on an individual can be described by two basic stages:

1. (*First Stage*) A person inhales some bacteria, and these enter the alveoli. There, some alveolar macrophages, which are already activated, will attempt to kill the pathogens by engulfing them. If the alveolar macrophages fail to destroy the inhaled bacilli, the later will reproduce inside the macrophages until they explode. This will attract monocytes from the bloodstream, which will ingest the bacilli released from the alveolar macrophages. Since these monocytes are not activated, they cannot destroy the bacilli they engulf. Thus, these bacilli will reproduce inside the new immature macrophages. In time, there will be a greater accumulation of bacteria and non-activated macrophages in the site of infection.

2. (*Second Stage*) The reproduction of bacteria stops abruptly at the beginning of the second stage of a tuberculosis infection. In this stage, infected macrophages present the antigen of Mycobacterium tuberculosis to specific T lymphocytes. These lymphocytes recognize the antigen and become activated. Following the activation of a T cell proceeds

the expansion of the population of activated T lymphocytes. These cells clone themselves producing more activated T cells until there are enough cells to deal with the infection. These cells may be of two types: helper T cells and cytotoxic T cells. The first ones will secrete lymphokines that activate macrophages in order to enable them to kill the bacteria they ingest. The second ones will produce lymphokines and other substances that will kill macrophages in which bacilli are reproducing. This stops the reproduction of bacteria inside the macrophages until other non-activated macrophages ingest the released bacilli or until activated macrophages engulf and destroy these bacteria. The interplay between these two types of responses of the immune system against the pathogen is what determines the fate of the disease, see [7].

For a detailed discussion on the progression of the TB infection see [1],[2], and [7].

Our model takes into account the *macrophage-activating response* described earlier, in which activated T cells secrete lymphokines that activate macrophages. For simplicity, the *tissue–damaging* response, i.e., the destruction of infected macrophages, is not considered in this model. We shall consider this type of response in a follow up paper.

We also assume that the infected person has inhaled some bacteria and that these organisms have reached the alveoli. The model does not account for the spread of the infection to other parts of the body, outside the lung of the infected individual.

We assume that macrophages go from their original state to the infected state, and, from there, to the activated state. T cells go from their original state to the activated state. Once a macrophage or T cell has reached a certain state, it either stays there or moves to the next state. They never move to a previous state. For example, they never move from the activated state to their original state.

The six populations in our model, in $cells\ per\ mm^{-3}$, are as follows:

$$\begin{aligned} M(t) &= \text{non-infected and non-activated macrophage,} \\ M_i(t) &= \text{infected and non-activated macrophage,} \\ M_a(t) &= \text{activated macrophage,} \\ T(t) &= \text{non-activated T cells,} \\ T_a(t) &= \text{activated T cells,} \\ P(t) &= \text{bacteria.} \end{aligned}$$

In Figure 1, we show the compartment diagram for the model. In the diagram, we represent: the birth rates by β's, the death rates by δ's, the transitional rates from one population to another by ϵ's, and the reproduction or attraction rates for a given population by r's.

We assume that the attraction rate of the macrophage in the presence of pathogens is governed by a predator-prey process, thus we model it by a logistic-type function $\hat{r}_M$, defined as

$$\hat{r}_M(M) = r_M \left(1 - \frac{M}{M_\infty}\right),$$

where r_M $(cells\ days^{-1})$ is the macrophages attraction rate and M_∞ $(cells\ mm^{-3})$ represents the maximum carrying capacity for the population of macrophage. Similarly, we model the bacteria's reproduction by using a logistic-type function $\hat{r}_P$, defined as

$$\hat{r}_P(P) = r_P \left(1 - \frac{P}{P_\infty}\right),$$

where r_P $(cells\ days^{-1})$ is the bacteria reproduction rate and P_∞ $(cells\ mm^{-3})$ represents the maximum carrying capacity for the population of bacteria. We assume that the reproduction rate for the activated T cells in the presence of infected macrophage is governed by an enzyme-substrate process. Thus we model it by using Michaelis-Menten kinetic, see [11], i.e.

$$r_T \frac{M_i}{(c_T + M_i)},$$

where r_T is the T cells reproduction rate $(cells\ days^{-1})$ and c_T $(cells\ mm^{-3})$ is the Michaelis constant. As infected macrophages die or explode, bacteria are liberated at the rate, $N\delta_{M_i} + Lg$, where N and L are the average number of bacteria per macrophage when it dies or explodes, respectively, and g is the explosion rate of infected macrophage. The constant η represents the rate at which activated macrophages kill bacteria. The resulting mathematical model for the tuberculosis infection described schematically in Figure 1 is given by:

$$
\begin{aligned}
\frac{dM}{dt} &= \beta_M + r_M \left(1 - \frac{M}{M_\infty}\right) P - \delta_M M - \epsilon_M P M, \\
\frac{dM_i}{dt} &= \epsilon_M M P - \delta_{M_i} M_i - g M_i - \epsilon_{M_i} T_a M_i, \\
\frac{dM_a}{dt} &= \epsilon_{M_i} T_a M_i - \delta_{M_a} M_a, \\
\frac{dT}{dt} &= \beta_T - \delta_T T - \epsilon_T M_i T, \qquad (1) \\
\frac{dT_a}{dt} &= \epsilon_T M_i T + r_T \frac{M_i}{c_T + M_i} T - \delta_T T_a, \\
\frac{dP}{dt} &= r_P \left(1 - \frac{P}{P_\infty}\right) M_i + N \delta_{M_i} M_i + L g M_i - \delta_P P - n \epsilon_M M P - \eta M_a P.
\end{aligned}
$$

The other parameters in (1) have the following meanings and units:

β_M, $\beta_T =$ birth rates of macrophages and T cells respectively ($cells\ mm^{-3} days^{-1}$);

ϵ_M, ϵ_{M_i}, $\epsilon_T =$ migration rates of $M(t)$ into $M_i(t)$, $M_i(t)$ into $M_a(t)$, and $T(t)$ into $T_a(t)$ respectively ($cells\ mm^3 days^{-1}$);

$\delta =$ with the corresponding subscript denotes death rate for the corresponding population ($cells\ days^{-1}$);

$r_M =$ denotes an attraction rate for the macrophage population ($cells\ days^{-1}$);

r_P, $r_T =$ denote reproduction rates for the corresponding population ($cells\ days^{-1}$);

$g =$ explosion rate of infected macrophage ($cells\ days^{-1}$);

$n =$ average number of engulfed bacteria by a macrophage (dimensionless);

$\eta =$ rate at which bacteria are killed by activated macrophage ($cells\ mm^3 days^{-1}$);

$N =$ average number of bacteria per macrophage when it dies (dimensionless);

$L =$ average number of bacteria per macrophage when it explodes (dimensionless).

3 Existence and Stability of Equilibrium Points

In this section we study the existence and stability of equilibrium points for the system (1). In particular we show that an equilibrium point representing an infection's free state exists for all permissible values of the parameters in the problem and find conditions on the parameters that guarantee the stability of this point. Moreover, we prove the existence of a surface of infectious equilibrium points bifurcating at the point at which the infection's free state looses stability.

The equilibrium points of the system (1) are given by the solutions of

$$\begin{aligned}
&\beta_M + r_M \left(1 - \tfrac{M}{M_\infty}\right) P - (\delta_M + \epsilon_M P) M = 0, \\
&\epsilon_M M P - \left[\delta_{M_i} + g + \epsilon_{M_i} T_a\right] M_i = 0, \\
&\epsilon_{M_i} T_a M_i - \delta_{M_a} M_a = 0, \\
&\beta_T - (\delta_T + \epsilon_T M_i)\, T = 0, \\
&\left(\epsilon_T + \frac{r_T}{c_T + M_i}\right) M_i T - \delta_T T_a = 0, \\
&\left[r_P \left(1 - \tfrac{P}{P_\infty}\right) + N\delta_{M_i} + Lg\right] M_i - (\delta_P + n\epsilon_M M + \eta M_a)\, P = 0.
\end{aligned} \tag{2}$$

Note that if $P = 0$, it is easy to see that a solution of the system (2) is given

by

$$M = \frac{\beta_M}{\delta_M} \equiv M_0 \quad , \quad T = \frac{\beta_T}{\delta_T} \equiv T_0 \quad , \quad M_i = M_a = T_a = 0. \tag{3}$$

This solution represents an *infection's free state*. We study now the stability of this solution and the existence of states of infection in which $P \neq 0$.

The derivative of the right-hand side of (1) (the Jacobian matrix) evaluated at (3) is now given by

$$\begin{bmatrix} -\delta_M & 0 & 0 & 0 & 0 & r_M\left(1-\frac{M0}{M_\infty}\right) - \epsilon_M M_0 \\ 0 & -\delta_{M_i} - g & 0 & 0 & 0 & \epsilon_M M_0 \\ 0 & 0 & -\delta_{M_a} & 0 & 0 & 0 \\ 0 & -\epsilon_T T_0 & 0 & -\delta_T & 0 & 0 \\ 0 & \left(\epsilon_T + \frac{r_T}{c_T}\right) T_0 & 0 & 0 & -\delta_T & 0 \\ 0 & N\delta_{M_i} + gL + r_P & 0 & 0 & 0 & -\delta_P - n\epsilon_M M_0 \end{bmatrix} \tag{4}$$

If we interchange rows two and five and simultaneously columns two and five of this matrix, we find that the eigenvalues of (4) are given by $-\delta_M$, $-\delta_{M_a}$, $-\delta_T$ (double), and those of the 2×2 matrix

$$\begin{bmatrix} -\delta_{M_i} - g & \epsilon_M M_0 \\ N\delta_{M_i} + gL + r_P & -\delta_P - n\epsilon_M M_0 \end{bmatrix} \tag{5}$$

An easy computation now shows that the remaining two eigenvalues of (4) are given by:

$$\frac{1}{2}\left[-\left(\delta_P + \delta_{M_i} + g + n\epsilon_M M_0\right) \pm \sqrt{d} \right] \tag{6}$$

where

$$d = \left[\left(\delta_P - \delta_{M_i} - g + n\epsilon_M M_0\right)^2 + 4\epsilon_M M_0 (N\delta_{M_i} + gL + r_P) \right].$$

Thus all eigenvalues of (4) are negative except the one corresponding to the plus sign in (6) which is negative if and only if

$$\frac{\epsilon_M \beta_M (g(L-n) + \delta_{M_i}(N-n) + r_P)}{\delta_M \delta_P (\delta_{M_i} + g)} < 1. \tag{7}$$

If we let

$$R = \frac{\epsilon_M \beta_M (g(L-n) + \delta_{M_i}(N-n) + r_P)}{\delta_M \delta_P (\delta_{M_i} + g)}, \tag{8}$$

we have that (3) is an asymptotically stable equilibrium point if $R < 1$ and unstable if $R > 1$. Moreover, since the only eigenvalue that can change sign is simple, and the explicit form (6) guarantees that the transversality condition of multiparameter bifurcation theory is satisfied, we get that (2) has a whole surface of solutions with $P \neq 0$. We summarize our results so far in the following theorem.

Theorem 3.1. *The equilibrium point (3) of the system (1) representing an infection's free state of the system is asymptotically stable if* $R < 1$ *and unstable if* $R > 1$. *Moreover, bifurcating from the trivial branch (3) at the surface where* $R = 1$ *there exists a ten-dimensional surface of solutions of (2) with* $P \neq 0$.

Proof: Let $\vec{\lambda} = (\epsilon_M, \beta_M, \ldots)$ be the vector of the ten parameters appearing in the definition of R. Let $\{\sigma_1(\vec{\lambda}), \ldots, \sigma_6(\vec{\lambda})\}$ be the set of eigenvalues of (4) where we assume that $\sigma_6(\vec{\lambda})$ corresponds to the one with the plus sign in (6), and the other eigenvalues are negative. Note that $R = 1$ if and only if $\sigma_6(\vec{\lambda}) = 0$. Let

$$\mathcal{E} = \{\vec{\lambda} : \sigma_6(\vec{\lambda}) = 0\}.$$

For any $a > 0$, let $\vec{s} : [-a, a] \to \mathbb{R}^{10}$ be a smooth curve that crosses $\mathcal{E}$ *transversely*, i.e.,

$$\sigma_6(\vec{s}(0)) = 0 \quad , \quad \nabla\sigma_6(\vec{s}(0)) \cdot \vec{s}\,'(0) \neq 0. \tag{9}$$

Then according to [12], Corollary (2.50), a ten dimensional surface of non trivial solutions of (3) bifurcates from $\mathcal{E}$ provided that $h(t) \equiv \sigma_6(\vec{s}(t))$ changes sign at $t = 0$. But by Taylor's theorem

$$\begin{aligned} h(t) &= h(0) + h'(0)t + o(t), \\ &= \nabla\sigma_6(\vec{s}(0)) \cdot \vec{s}\,'(0)t + o(t), \end{aligned} \tag{10}$$

which changes sign at $t = 0$ if $\vec{s}(t)$ satisfies (9). □

The solutions with $P \neq 0$ predicted by Theorem (3.1) represent infectious steady states for the system (1).

Let us write R as

$$R = R_M R_{M_i} R_P, \tag{11}$$

where

$$R_M = \frac{\epsilon_M \beta_M}{\delta_M},$$

$$R_{M_i} = \frac{\frac{g(L-n)+\delta_{M_i}(N-n)}{r_P} + 1}{\delta_{M_i} + g},$$

and

$$R_P = \frac{r_P}{\delta_P}.$$

In view of (11), R relates the growth rate of the populations of macrophages and bacteria with certain rates for the explosion and death of infected macrophages.

4 Numerical Simulations

We describe in this section some numerical simulations for the system (1). The numerical environment we used was MATLAB, version 5.2 in particular the routine ode45 and ode15s. Both routines employ adaptive Runge-Kutta solvers, the ode15s been specially designed for handling stiff problems.

The choice of the parameter values for our model is not an easy task! In Table 1, we show the parameter and input values for system (1). See the discussion below for the literature references and the criteria we used in choosing these values.

We start our simulations with a macrophage population of 500 $cells\ per\ mm^{-3}$, and with a bacteria population of 100 $cells\ per\ mm^{-3}$. The population of helper T cells is approximately of 1000 $cells\ per\ mm^{-3}$ (see [8]), thus we choose 1000 $cells\ per\ mm^{-3}$ to start our simulations.

The death rate for T cell is $\delta_T = 0.02$, see [9] and [10]. The ratio of the macrophage death rate to the T cell death rate is 200 (see [10]), therefore $\delta_M = (200)(0.02) = 4$. Moreover, we assume that $\delta_{M_i} = \delta_{M_a} = \delta_M$.

We choose the birth rate of T cell such that in the absence of infected macrophages the population of T cells maintains its initial value $T(0)$. Thus $\beta_T = (0.02)(1000) = 20$.

The turnover rate for macrophage and T cell interaction is approximately 5.5 $hrs.$, see [10] and [13]. To estimate the activation rate of T cell, ϵ_T, we take the reciprocal of the turnover rate (in days) and divide it by the T cell

average population. Similarly, we estimate the activation rate of infected macrophage, ϵ_{M_i}, by taking the reciprocal of the turnover rate (in days) and divide it by the macrophage average population.

Now we consider two cases where the parameters β_M, r_M, r_P, and δ_P are chosen such that we get different results for the dynamics of the macrophage and bacteria populations.

As a first case, we choose r_P and δ_P such that $R_P > 1$ in (11). That means that the bacteria population reproduces faster than it dies. We choose $\delta_P = 2 \times 10^{-2}$ and $r_P = 2$. Then we choose β_M such that $R > 1$ in (8). Figure (2) shows the macrophage populations, Figure (3) shows the bacteria population, and Figure (4) shows the T cell populations for a time period of 50 days. As can be verified by substituting in the system (2), this solution approaches the equilibrium point

$$\begin{aligned} M = 628.93 \quad , \quad M_i = 3.55 \quad , \quad M_a = 16.89, \\ T = 563.72 \quad , \quad T_a = 436.38 \quad , \quad P = 648.03. \end{aligned} \tag{12}$$

For the second case, we choose $\delta_P = 2$ and $r_P = 2 \times 10^{-1}$ such that $R_P < 1$ in (11). Then we choose β_M such that $R < 1$ in (8). Figure (5) shows the macrophage populations, Figure (6) shows the bacteria population, and Figure (7) shows the T cell populations for a time period of 50 days. This time the solution converges to the infection's free equilibrium point (3).

Our final simulation illustrate some of the kind of solutions that (1) admits. A *Hopf bifurcation* for the system (1) occurs at an equilibrium point, i.e., a solution of (2), at which bifurcation into a periodic solution occurs.

These points are characterized by the existence of two complex conjugate pure imaginary eigenvalues of the Jacobian matrix J of the left-hand side of the system (2). If all the eigenvalues of J are nonzero and only two are pure imaginary and they cross the imaginary axis with nonzero slope at the equilibrium point in question, then one has a Hopf bifurcation at that point (see [14]). Since the eigenvalues of (4) are all real, any Hopf bifurcation for the system (2) must occur at a nontrivial solution (like those predicted by Theorem (3.1)).

The parameters used in this case are those in Table (1) with

$$\beta_M = 200 \quad , \quad r_M = 10 \quad , \quad \delta_P = 0.178.$$

Using a numerical algorithm for computing Hopf bifurcations given in [15] (pp. 72-73), we vary numerically the parameter r_P. We found numerically that the system (1) exhibits a Hopf bifurcation at $r_P = 2.121$ approximately. The non-trivial steady state corresponding to this Hopf bifurcation is given by

$$\begin{aligned} M = 460.3866 \quad , \quad M_i = 2.1601 \quad , \quad M_a = 7.5397, \\ T = 679.8520 \quad , \quad T_a = 320.2198 \quad , \quad P = 312.1986. \end{aligned} \tag{13}$$

For values of r_P slightly less than 2.121, the steady state solution is stable while for values slightly bigger than 2.121, a stable periodic solution appears and the non-trivial steady state becomes unstable. As initial conditions for these simulations we use the values in (13). In Figure (8) we can see the time evolution of the system approaching a stable non-trivial steady state solution corresponding to $r_P = 2.12$, that is close but not equal to (13) (we show only

the population of bacteria versus that of infected macrophage). In Figure (9) we have that the evolution of the system now approaches a stable periodic solution corresponding to $r_P = 2.2$. This solution represents a type of state of latent infection but in dynamical equilibrium. In this case the populations of infected macrophage and bacteria behave similar to a predator-prey system.

5 Summary and Conclusions

We developed a model for the dynamic interaction between macrophage, T cell, and mycobacterium tuberculosis based on six populations of them. This model incorporates logistic and Michaelis-Menten kinetics for reproduction rates.

We tested the model by using some parameter values from the available literature together with the stability condition for the infection's free state. When the parameter values were set to satisfy that condition the simulation, as predicted by Theorem (3.1), converged to the infection's free equilibrium point (3). On the other hand, when the parameters values violated that condition, the simulation converged to an equilibrium point different to the infection's free equilibrium point. Also we showed numerically that the proposed model can exhibit Hopf bifurcations. The periodic solutions appearing at a Hopf bifurcation as well as the infectious equilibrium points, could be interpreted as a state of latent infection in dynamical equilibrium or constant in time.

We proved in Theorem (3.1) that an infection's free equilibrium point exists for all permissible values of the parameters in the problem and found conditions on the parameters that guarantee the stability of this point. Moreover, we proved the existence of a surface of infectious steady state points bifurcating at the point at which the infection's free state looses stability.

A major problem in the study of mathematical models of populations is the lack of data for many of the parameters used in the model. These parameters are usually only known to have values within certain ranges and many of them like the r's, are unknown. This is where an analysis like that in Theorem (3.1) becomes very valuable because we get information about qualitative properties of the system without restricting the values or ranges of the parameters involved. To get further information on the stability of the nontrivial bifurcating branches in Theorem (3.1), one needs to compute higher order derivatives of the left hand side of (2) to determine the type of bifurcation diagram at hand.

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Figure Legends

Figure 1: Compartment diagram for a six population model of tuberculosis.

Table 1: Parameter and input values for system (1). See text for the literature references and the criteria we used in choosing these values.

Figure 2: Macrophage population, divided by the initial value $M(0)$, on the left and infected and activated macrophage populations on the right for the data in Table 1 with $R_P > 1$.

Figure 3: Bacteria population divided by its initial value for the data in Table 1 with $R_P > 1$.

Figure 4: Populations of T, T_a, and their sum for the data in Table (1) with $R_P > 1$.

Figure 5: Macrophage population, divided by the initial value $M(0)$, on the left and infected and activated macrophage populations on the right for the data in Table 1 with $R_P < 1$.

Figure 6: Bacteria population divided by its initial value for the data in Table 1 with $R_P < 1$.

Figure 7: Populations of T, T_a, and their sum for the data in Table (1) with $R_P < 1$.

Figure 8: Dynamics of the system (1) converging to a stable infectious state for $r_P = 2.12$.

Figure 9: Dynamics of the system (1) converging to a stable periodic solution for $r_P = 2.2$.

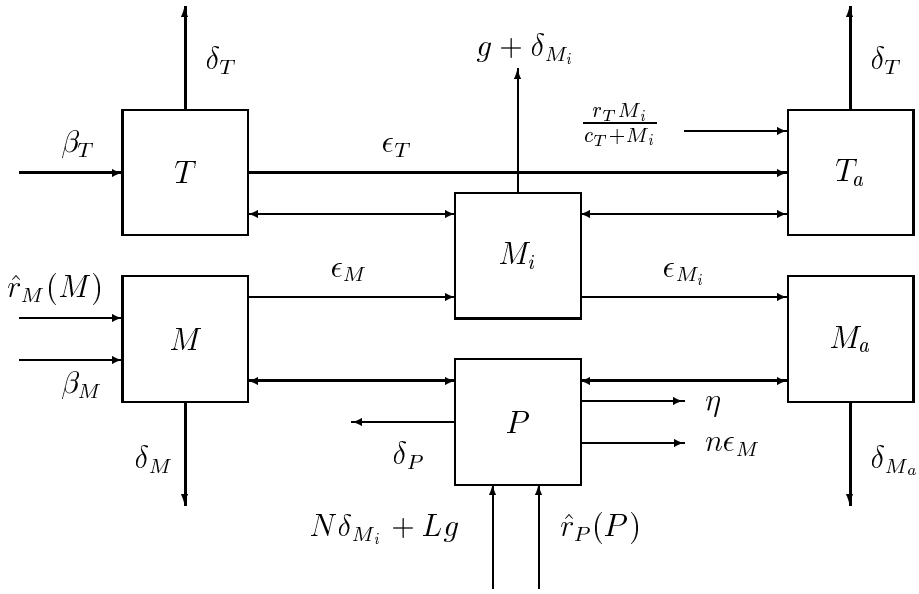
δ_T
$g + \delta_{M_i}$
δ_T
β_T
T
ϵ_T
$\frac{r_T M_i}{c_T + M_i}$
T_a
M_i
$\hat{r}_M(M)$
ϵ_M
ϵ_{M_i}
M
M_a
β_M
P
η
$n\epsilon_M$
δ_M
δ_P
δ_{M_a}
$N\delta_{M_i} + Lg$
$\hat{r}_P(P)$

Figure 1:

Parameter	Value
δ_M	$4\ cells\ per\ d^{-1}$
ϵ_{M_i}	$4.36 \times 10^{-2}\ cells\ per\ mm^3 d^{-1}$
ϵ_M	$3 \times 10^{-4}\ cells\ per\ mm^3 d^{-1}$
M_∞	$10^3\ cells\ per\ mm^{-3} d^{-1}$
δ_T	$2 \times 10^{-2}\ cells\ per\ d^{-1}$
β_T	$2 \times 10^1\ cells\ per\ mm^{-3} d^{-1}$
ϵ_T	$4.36 \times 10^{-3}\ cells\ per\ mm^3 d^{-1}$
r_T	$10^{-4}\ cells\ per\ d^{-1}$
c_T	$10^2\ cells\ per\ mm^{-3} d^{-1}$
η	$10^{-4}\ cells\ per\ mm^3 d^{-1}$
P_∞	$10^2\ cells\ per\ mm^{-3}$
$\delta_{M_i} = \delta_{M_a}$	δ_M
L	15
N	15
n	3
g	$2\ cells\ per\ d^{-1}$
$r_p, \delta_P, \beta_M, r_M$	Vary
$M(0)$	$500\ cells\ per\ mm^{-3}$
$T(0)$	$1000\ cells\ per\ mm^{-3}$
$P(0)$	$100\ cells\ per\ mm^{-3}$
$M_i(0) = M_a(0) = T_a(0)$	0

Table 1:

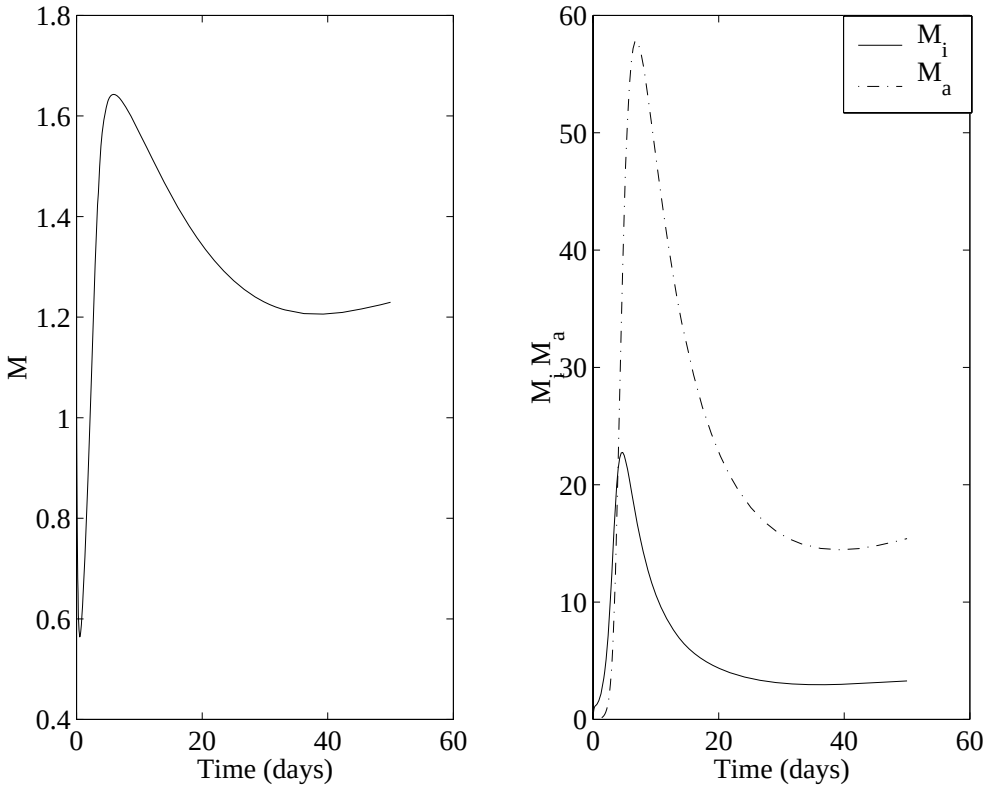

Figure 2:

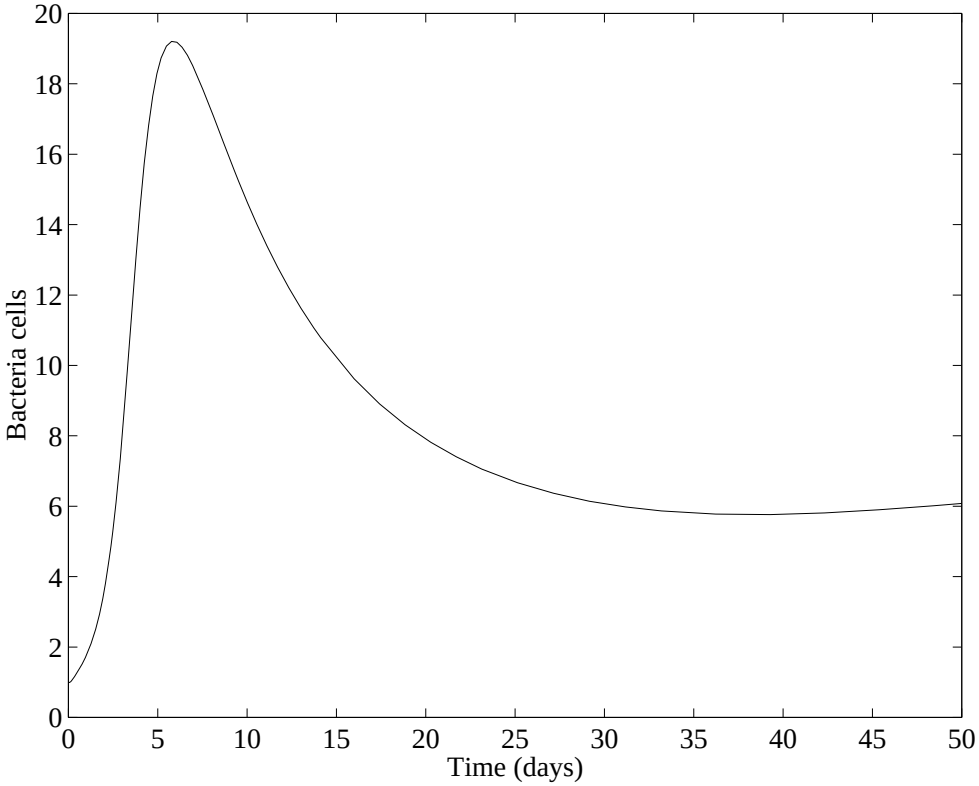
Bacteria cells
Time (days)
0
2
4
6
8
10
12
14
16
18
20
0
5
10
15
20
25
30
35
40
45
50

Figure 3:

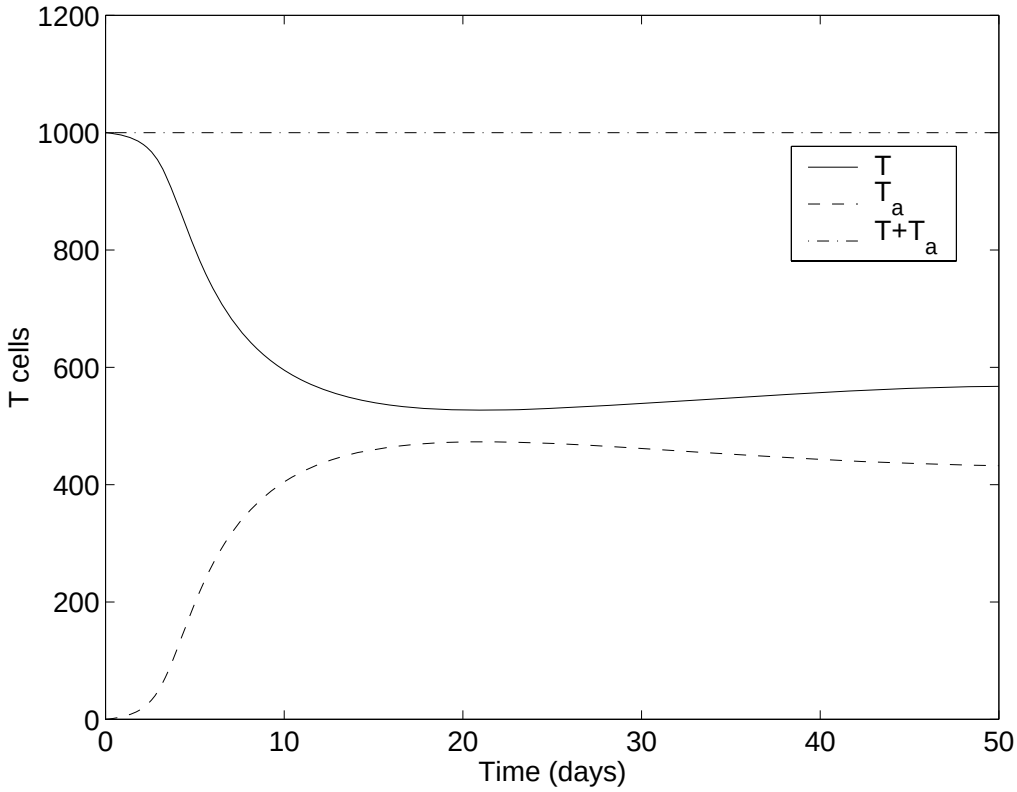
1200
1000
800
600
400
200
0
T cells
0
10
20
30
40
50
Time (days)
T
T_a
T+T_a

Figure 4:

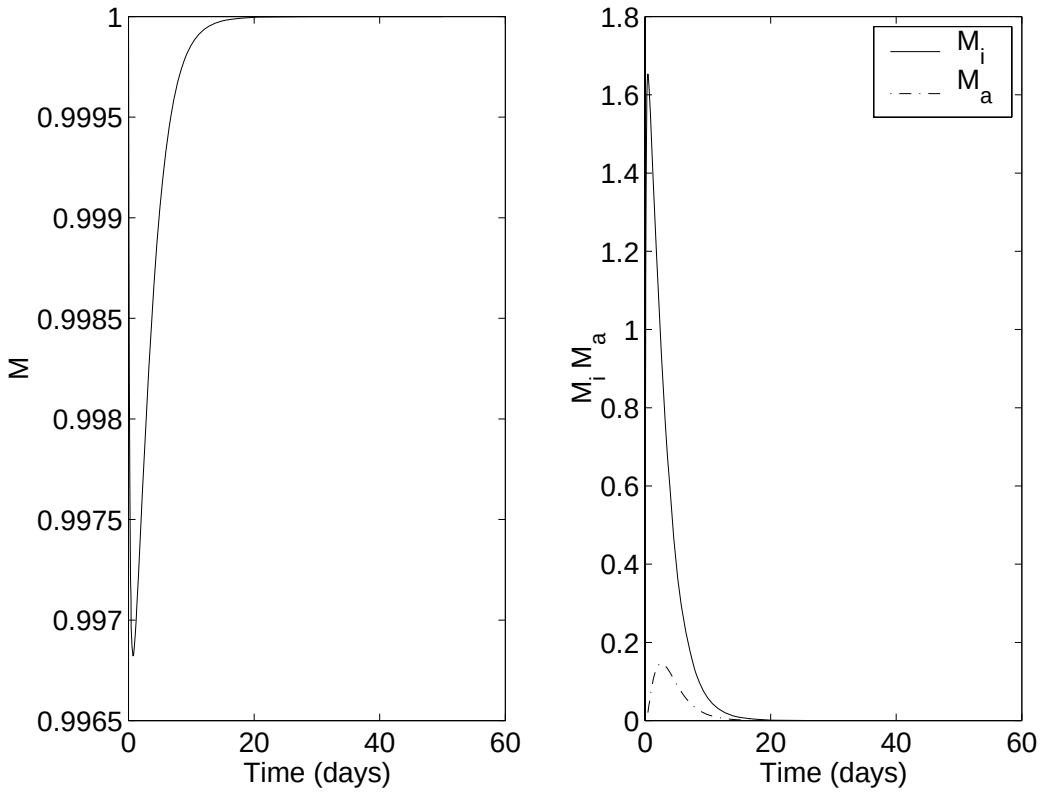
1
0.9995
0.999
0.9985
0.998
0.9975
0.997
0.9965
M
0
20
40
60
Time (days)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
M_i M_a
M_i
M_a
0
20
40
60
Time (days)

Figure 5:

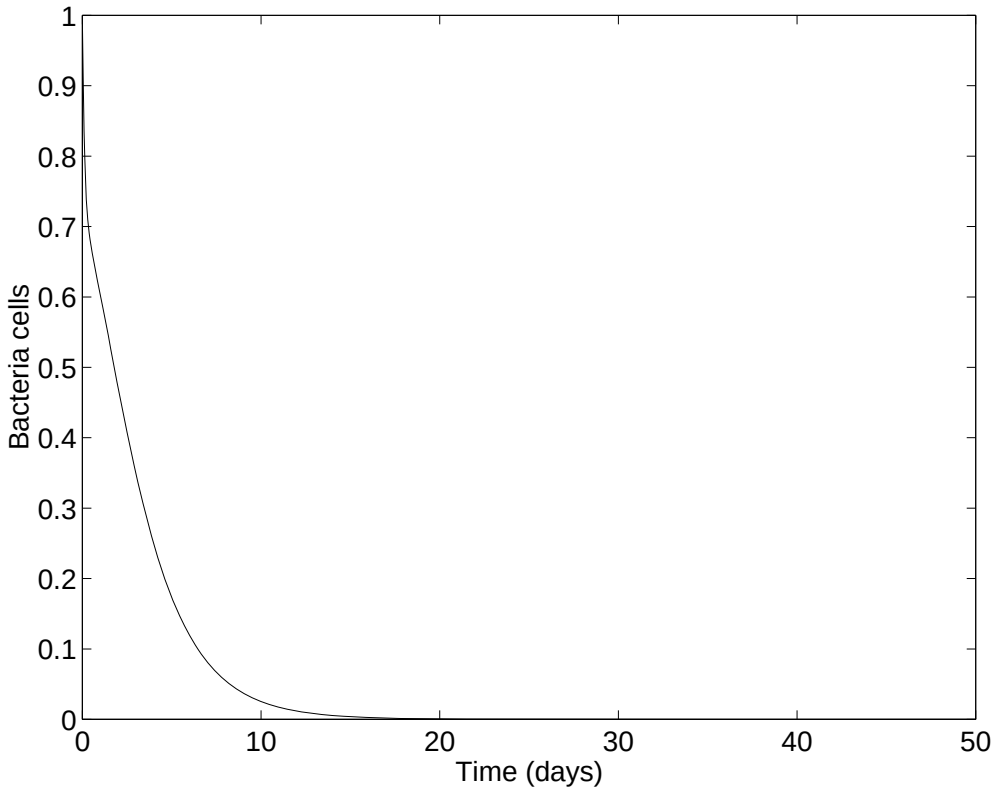
Bacteria cells
Time (days)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50

Figure 6:

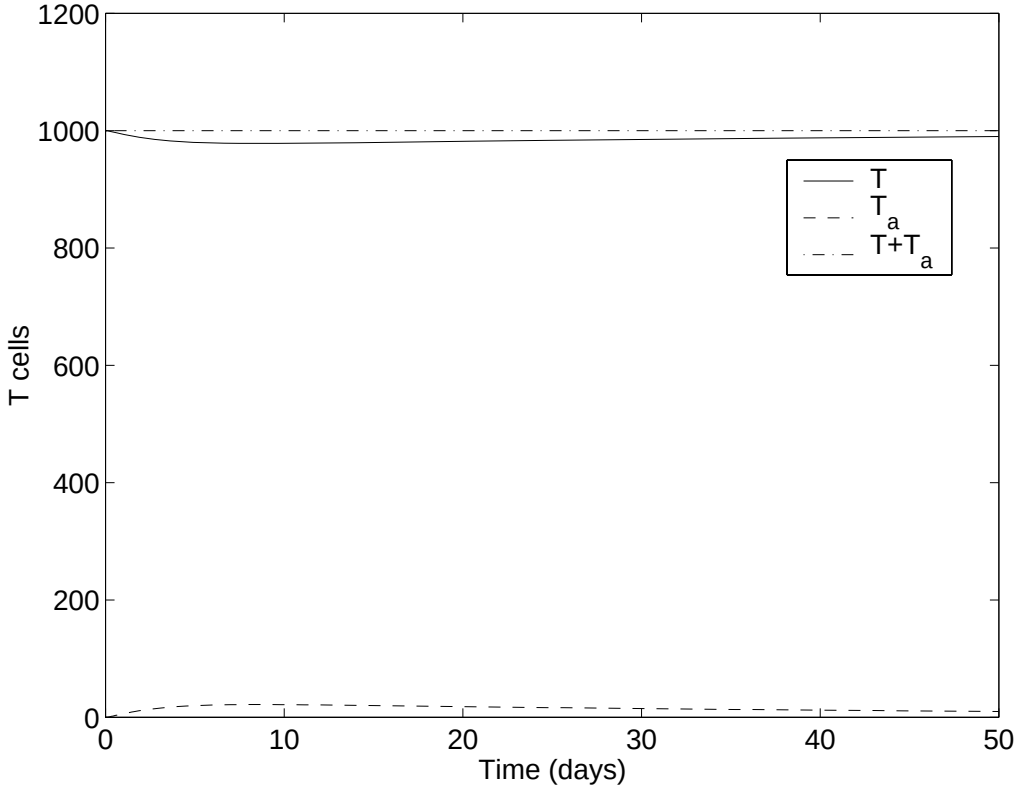
1200
1000
800
600
400
200
0
T cells
0
10
20
30
40
50
Time (days)
T
T_a
T+T_a

Figure 7:

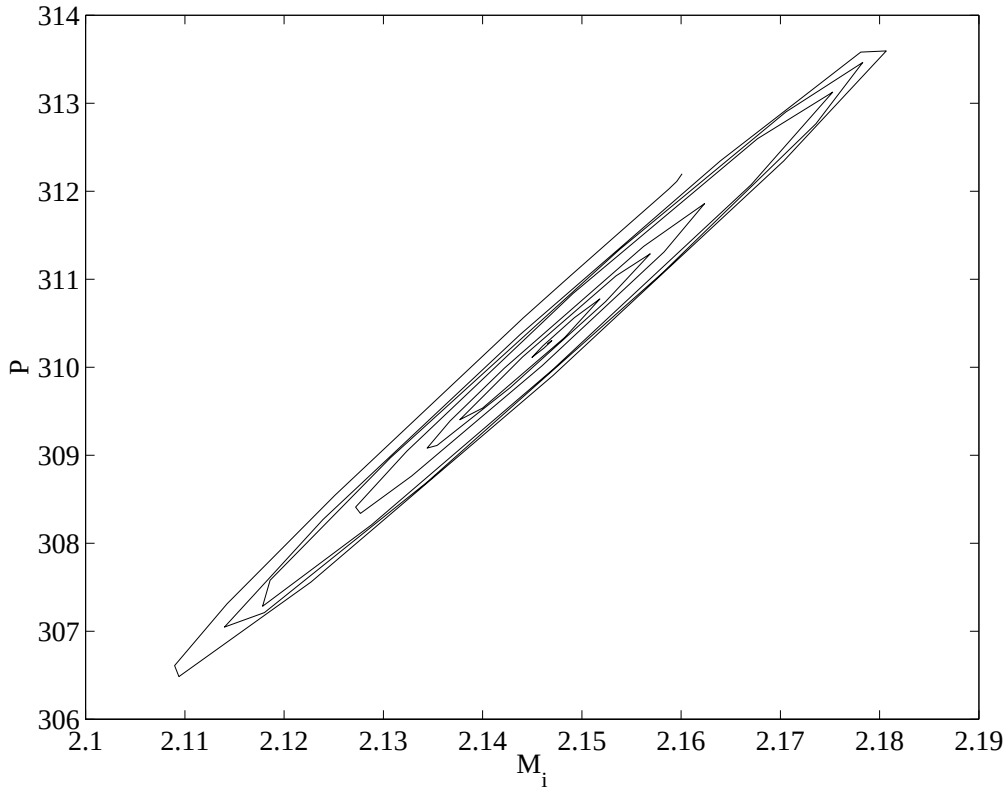
314
313
312
311
310
309
308
307
306
P
2.1
2.11
2.12
2.13
2.14
2.15
2.16
2.17
2.18
2.19
M_i

Figure 8:

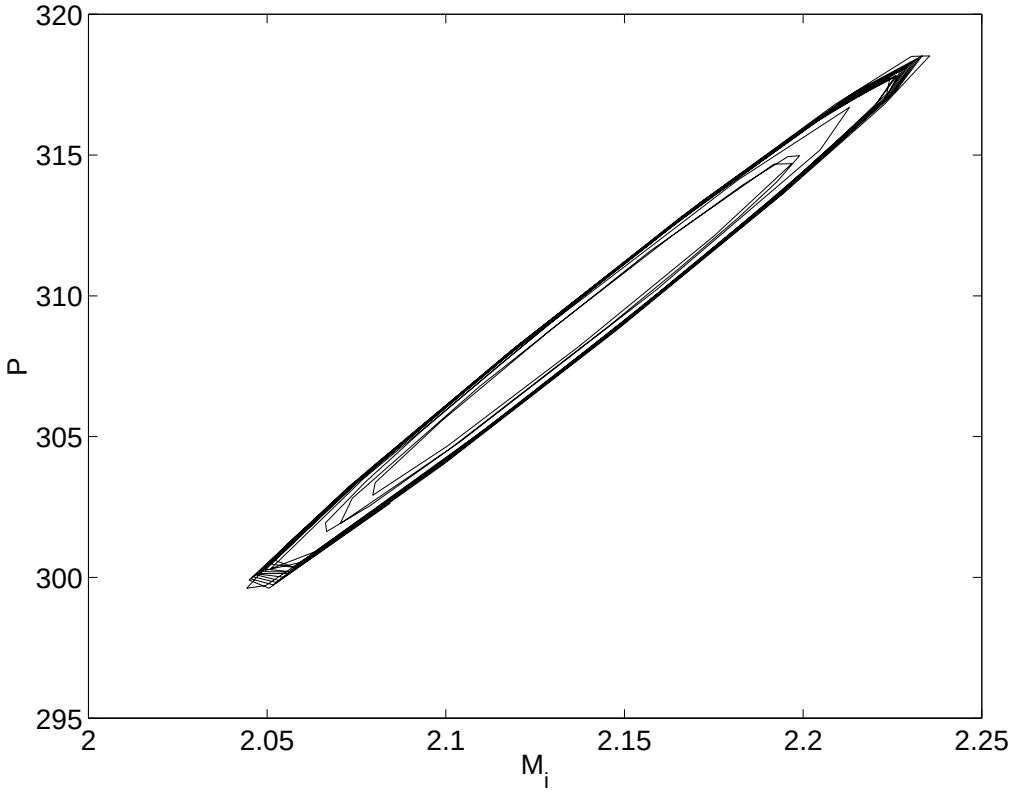

Figure 9: