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## ROLE OF MACROPHAGE IN THE DISEASE DYNAMICS OF CUTANEOUS LEISHMANIASIS: A DELAY INDUCED MATHEMATICAL STUDY

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**Abstract.** Leishmaniasis is endemic in 88 countries throughout Africa, Asia, Europe, and North and South America. It is a vector borne zoonosis with important animal reservoirs and has a two stage life cycle-within animal vector and mammalian host. In this research article, a mathematical model is considered to analyze the disease dynamics of Leishmaniasis consisting susceptible (uninfected) macrophage cell, early stage infected (promastigotes) macrophage cell, late stage infected (amastigotes) macrophage cell and parasite population. The focus is to study the progression of the disease caused by pathogen within mammalian cycle. To study the model in broader aspect, a time delay is introduced into the system as there is a time lag in the interaction between uninfected macrophage cell and parasite population and spread of the disease. Theoretical analysis and numerical simulations reveals that, the delay induced system exhibits changes in the progression pattern of infected and uninfected macrophage cell and parasite population. Control effect i.e. drug dosing can minimize the phagocytic state of macrophages and suppress the state change from promastigotes into amastigotes inside macrophages. Moreover delay induced control give better result than proposed model with control as healthy macrophage cell population reaches more stable nature. Optimal control theory facilitates a cost effective drug dose strategy that increases the healthy macrophage cell population, whereas decreases rest of the population.

**Keywords:** Vector borne disease; Cutaneous leishmaniasis; Leishmania; Macrophage; Promastigotes.

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## 1. Introduction

Leishmaniasis is a vector borne diseases, which is caused by protozoan parasite of the genus *Leishmania* [1]. Infected female *phlebotomine* sandflies are responsible for disease transmission [2, 3]. Leishmaniasis is endemic globally in eighty eight countries [4, 5]. About ninety percent of the global cases of Cutaneous Leishmaniasis come from Afghanistan, Algeria, Iran, Iraq, Pakistan, Brazil, Peru etc [6]. There are an estimated twelve million cases globally with 1.5 to 2 million new cases in each year [4]. Leishmaniasis is also manifested in India (mainly in provinces of Bihar and Rajasthan). There are four clinical forms for Leishmaniasis and these are termed as Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (known as Espundia), Visceral Leishmaniasis (known as Kala-azar) and Post Kala-azar Dermal Leishmaniasis (PKDL). In zoonotic transmission, animals are responsible for distributing the *Leishmania* parasites. Otherwise, in anthroponotic form, sandfly vector are liable for infecting mammalian host including human [7, 8].

The parasite has a digenetic life cycle with an extracellular developmental stage in the insect vector, a female *phlebotomine* sandfly, and a developmental stage in mammals, which is mostly intracellular. In sandflies, development of the parasite occurs in the alimentary canal with the formation of a motile, flagellated and elongated form termed as 'promastigote'. The promastigote matures in the insect midgut into an infective metacyclic promastigote. Inoculation into the mammalian host occurs when sandflies feed on blood, which is a requirement for oviposition. A typical inoculum contains around 100 – 1000 metacyclic promastigotes which quickly become surrounded by leucocytes, particularly macrophages, neutrophils and dendritic cells. The parasites undergo a further transformation within these cells to form amastigotes. A morphological change occurs as the parasite takes on an ovoid shape with a short flagellum, hence the term 'amastigote'. The distribution and manifestations of the disease vary widely according to the parasite species and the underlying immune response of the host. However, a feature common to mammalian infection with all parasite species is that the infection is intracellular with parasites only briefly exposed to an extracellular environment at inoculation [9].

For parasite interaction with the host the *Leishmania* must affect both the adaptive and immune responses. Infected sandfly while active bloodmeal injects the parasites promastigote

stage into the human skin and its target and persist in the tissue macrophages. Promastigotes are phagocytized by macrophages and transform into non flagellated amastigotes [10], [11]. Amastigotes replicate and then spread either locally or via different tissues and infect additional macrophages. When an uninfected sandfly feeds blood on an infected host, then it becomes infected with the amastigotes [12] which transform back into promastigotes in the sandfly gut depending upon *Leishmania* species.

From a clinical point of view, the disease Cutaneous Leishmaniasis starts from small cutaneous nodules to mucosal tissue demolition. The fundamental treatment for Cutaneous Leishmaniasis is the pentavalent antimonial compounds [13, 14]. Oral and topical treatment are also employed in the treatment of the disease. For the complexity of disease, the controlling of parasite population in the macrophage cell is difficult in a realistic scenario.

Mathematical modeling of the processes, involved in parasite-host interactions, has become a global trend in the study of diseases, Leishmaniasis being no exception. A major part of the modeling work in this field is epidemiological [1, 7, 15]. There are many studies regarding the biology, epidemiology and immunology of leishmaniasis [1, 7, 15, 16, 17], yet there are fewer studies related to the evolution of the infection in animal models.

Dancik et al. [18] used a stochastic version model to study the immune response of mice to *L.major* infection to identify parameters that are important in changing the dynamics of the infection process, and to quantify the influence of those parameters. To study the dynamics of the disease propagation and its transmission in mammalian hosts, mathematical models are indispensable tools. Modeling of transmission dynamics of Cutaneous Leishmaniasis has been investigated by different workers. Luis et al., [1] has formulated a mathematical model considering the vector, host and reservoir population of American Cutaneous Leishmaniasis. Marcos et al., [19] developed a mathematical model of immune response in Cutaneous Leishmaniasis. Agyingi et al., [20] considered a SIS model that describes the transmission dynamics of Cutaneous Leishmaniasis. The model treats a vector population and several populations of different mammals. Ambit et al., [21] describe the morphological events during the cell cycle of *Leishmania major*.

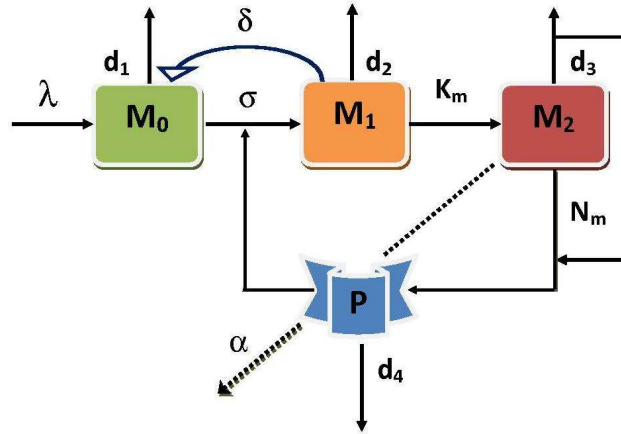
Recently, Stauch et.al. [22] have modeled the transmission dynamics of *L. donovani* in the Indian subcontinent deterministically by a system of ordinary differential equations. They have considered SIR type model which was modified with respect to the history of infection, considering five stages in the natural history of infection and time lags in treatment regime. Although, the works involving the delay differential are a recent development in Leishmaniasis, but the works is quite sporadic and not extensive. In recent times, a significant work is being done on the dynamics of Cutaneous Leishmaniasis using delay differential equations [23, 24]. Das et. al. [25] have studied the dynamics of American Cutaneous Leishmaniasis with delay. They have considered a delay in between infection and infectiousness for the reservoir hosts. The length of delay was estimated for preserving stability. Chaves [26] has shown that a delay between human infection with causative parasites exists and the start with clinical symptoms.

Langer et.al., [27] studied Leishmaniasis infection dynamics through a systems biology approach. The biological interrelations between variables, predictive simulations, sensitivity analysis were done to evaluate the significance of the system parameters, and an optimization problem was solved for minimizing the parasite load. This analysis contributes valuable information to the drug discovery pipeline for developing effective therapeutic methods against Leishmaniasis which is a striking overlapping interest with this article but a model is formulated which is based on delay differential equations considering only the mammalian cycle of the vector and optimal control approach.

The present investigation is based on the work of Nelson [28] through a modified version considering the role of the macrophage for developing the disease intracellularly. Another stage of infection is considered as there is a transformation from promastigote stage to amastigote stage and after that amastigote multiply in cells of various tissues. The focus is to study how parasite enters in the human body and then spreading intracellularly. The model has been analyzed through cytobiological interactions employing mathematical approach to explore the behavior of the disease. Finally, optimal drug dosing is applied to the macrophage cell and parasite population, to control the parasite population in the macrophage cell. Numerical simulations are in a good agreement with analytical results.

## **2. Formulation of the General Mathematical Model**

Cytology of macrophage cell has an enormous importance to study the disease dynamics of Cutaneous Leishmaniasis. Macrophage cells were divided into two classes such as susceptible macrophage cell and infected macrophage cell, where as the infected macrophage cells has two sub classes i.e., early stage infected macrophage cell and late stage infected macrophage cell. In this research article, a mathematical model is formulated which considers these four components : susceptible macrophage cell  $M_0(t)$ , early stage infected macrophage cell (promastigotes) denoted by  $M_1(t)$ , late stage infected macrophage cell (amastigotes) is defined as  $M_2(t)$  and parasite population  $P(t)$ . Now consider ( $\lambda$ ) a constant source rate of macrophage,  $\delta$  rate constant of change in macrophage status,  $\sigma$  rate of constant of infectivity, state change rate for macrophage (i.e. promastigotes to amastigotes stage) is denoted as  $K_m$ , burst size of amastigotes is put in the form as  $N_m$ . The compartmental model system and interactions across the different compartment is shown by the following schematic diagram.



From the above assumption, the developed model thus formulated as,

$$\begin{aligned}
 \frac{dM_0}{dt} &= \lambda + \delta M_1 - \sigma M_0 P - d_1 M_0, \\
 \frac{dM_1}{dt} &= \sigma M_0 P - \delta M_1 - d_2 M_1 - K_m M_1, \\
 \frac{dM_2}{dt} &= K_m M_1 - d_3 M_2, \\
 \frac{dP}{dt} &= N_m d_3 M_2 - d_4 P - \alpha P M_2,
 \end{aligned} \tag{2.1}$$

with the initial conditions  $M_0(0) > 0$ ,  $M_1(0) > 0$ ,  $M_2(0) > 0$  and  $P(0) > 0$ .

Here,  $d_1$ ,  $d_2$ ,  $d_3$  and  $d_4$  are the death rate of susceptible macrophage, death rate of infected macrophage in promastigote form, death rate of infected macrophage in amastigote form respectively and the loss of the parasite population is at a rate  $\alpha$  as parasite interact with the infected macrophage.

All the parameters and variables are real and non-negative. Thus, the system is bounded if the conditions below are satisfied:

$$K_m > \frac{d_1 d_4 (\delta + d_2)}{\sigma \lambda N_m - d_1 d_4}, \text{ and } \lambda > \frac{d_1 d_4}{\sigma N_m}.$$

## 2.1. Theoretical Analysis of the System

### Existence of Equilibria

In this system, there are two equilibrium points, infection free equilibrium which is given by

$$E_0 = (\bar{M}_0, \bar{M}_1, \bar{M}_2, \bar{P}) = \left( \frac{\lambda}{d_1}, 0, 0, 0 \right),$$

and another one is infected state equilibrium  $E^* = (M_0^*, M_1^*, M_2^*, P^*)$ ,

$$\text{where } M_0^* = \frac{\lambda - M_1^* (K_m + d_2)}{d_1}, M_1^* = \frac{d_3 d_4 P^*}{K_m (N_m d_3 - \alpha P^*)}, M_2^* = \frac{d_4 P^*}{(N_m d_3 - \alpha P^*)} \text{ and}$$

$$P^* = \frac{\sigma \lambda K_m N_m d_3 - d_1 d_3 d_4 \delta - d_1 d_3 d_4 (K_m + d_2)}{\sigma \lambda \alpha K_m + \sigma d_3 d_4 (K_m + d_2)}.$$

It is to be noted that  $\frac{N_m d_3}{\alpha P^*} > 1$  is the necessary condition for validity of above variables. The right hand side of the equation (2.1) is a smooth function of  $M_0$ ,  $M_1$ ,  $M_2$ ,  $P$  (the variables) and the parameters, as long as the quantities are non-negative, so local existence and uniqueness properties hold in the positive octant.

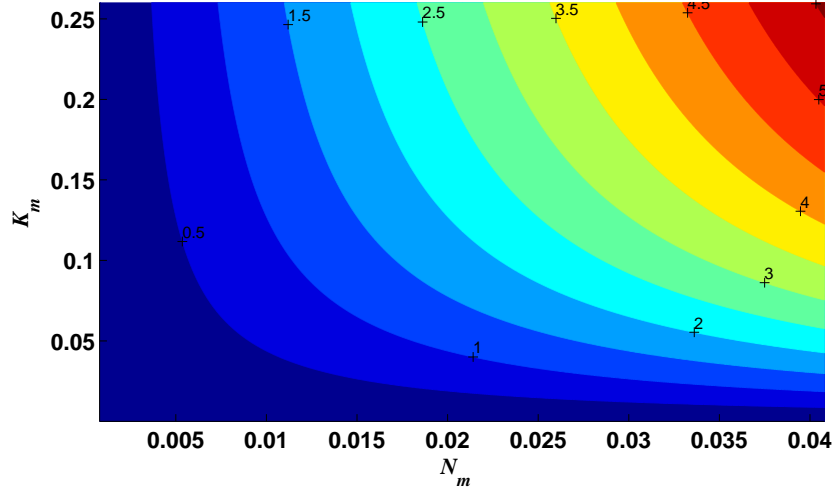


FIGURE 1. Contour plot of  $R_0$  as a function of  $K_m$  and  $N_m$ .

**Biological Interpretation:** If the state change factor ( $K_m$ ) remains below its threshold value then the system remains in its infection free situation. If state change factor increases and passes through its threshold value, then the system moves to infected state and disease persists.

## 2.2. Stability Analysis of Infection-free Equilibrium

The Jacobian matrix can be written as,

$$J|_{(\bar{M}_0, 0, 0, 0)} = \begin{pmatrix} -d_1 & \delta & 0 & -\frac{\sigma\lambda}{d_1} \\ 0 & -\delta - d_2 - K_m & 0 & -\frac{\sigma\lambda}{d_1} \\ 0 & -K_m & -d_3 & 0 \\ 0 & 0 & N_m d_3 & -d_4 \end{pmatrix}.$$

The characteristic polynomial of the above matrix is found as,

$$\det \begin{pmatrix} -d_1 - \xi & \delta & 0 & -\frac{\sigma\lambda}{d_1} \\ 0 & -\delta - d_2 - K_m - \xi & 0 & -\frac{\sigma\lambda}{d_1} \\ 0 & -K_m & -d_3 - \xi & 0 \\ 0 & 0 & N_m d_3 & -d_4 - \xi \end{pmatrix} = 0.$$

Thus,

$$\xi^3 + (\delta + d_2 + K_m + d_3 + d_4)\xi^2 + ((\delta + d_2 + K_m)(d_3 + d_4) + d_3d_4)\xi + (\delta + d_2 + K_m)d_3d_4 - \frac{\sigma\lambda}{d_1}K_mN_md_3 = 0.$$

The threshold condition is determined by the sign of constant term. It follows that

$$R_0 = \frac{\sigma\lambda K_m N_m}{(\delta + d_2 + K_m)d_1 d_4}. \quad (2.2.1)$$

Now, the following theorem can be obtained.

**Theorem 2.2.1.** *If  $R_0 < 1$ , infection-free equilibrium is stable, while if  $R_0 > 1$ , the infection-free equilibrium is unstable and the infected state equilibrium exists.*

The characteristic polynomial for the infected equilibrium is,

$$\begin{aligned} & (-\sigma P^* - d_1 - \xi) \left[ (-\delta - d_2 - K_m - \xi)(-d_3 - \xi)(-d_4 - \alpha M_2^* - \xi) + \right. \\ & \left. (\sigma M_0^* K_m (N_m d_3 - \alpha P^*)) \right] - \sigma P^* \delta [(-d_3 - \xi)(-d_4 - \alpha M_2^* - \xi)] \\ & + (\sigma P^*)(\sigma M_0^* K_m (N_m d_3 - \alpha P^*)) = 0. \end{aligned}$$

From above, it can written obtain that,

$$\xi^4 + a_1 \xi^3 + a_2 \xi^2 + a_3 \xi + a_4 = 0,$$

where,

$$\begin{aligned} a_1 &= \sigma P^* + \alpha M_2^* + d_1 + \delta + d_2 + K_m + d_3 + d_4 > 0, \\ a_2 &= (\sigma P^* + d_1)(d_2 + K_m + d_3 + d_4 + \alpha M_2^*) + (d_4 + \alpha M_2^* + d_3)(\delta + d_2 + K_m) \\ &\quad + d_3(d_4 + \alpha M_2^*) + d_1 \delta > 0, \\ a_3 &= (\sigma P^* + d_1)d_3(d_4 + \alpha M_2^*) + d_3(d_4 + \alpha M_2^*)(\delta + d_2 + K_m) \\ &\quad + (\sigma P^* + d_1)(d_2 + K_m)(d_4 + \alpha M_2^*) + d_1 \delta (d_4 + \alpha M_2^*) + \end{aligned}$$



$$d_3(\sigma P^* + d_1)(d_2 + K_m) + d_3 d_1 \delta - \sigma M_0^* K_m (N_m d_3 - \alpha P^*) > 0,$$

$$a_4 = (\sigma P^* + d_1)(d_2 + K_m) d_3 (d_4 + \alpha M_2^*) + d_3 d_1 \delta (d_4 + \alpha M_2^*)$$

$$- d_1 \sigma M_0^* K_m (N_m d_3 - \alpha P^*) > 0.$$

By applying Routh-Hurwitz criterion, the necessary and sufficient conditions for asymptotical stability are:

$$a_1 a_2 - a_3 > 0, a_1 a_2 a_3 - a_1^2 a_4 - a_3^2 > 0.$$

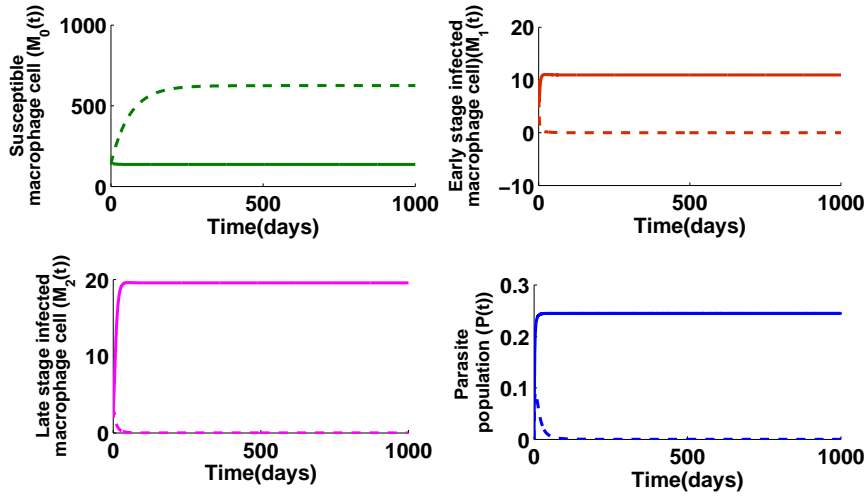


FIGURE 2. Population densities of the model variables with respect to time for infection free state when  $R_0 < 1$  (dotted line) and infected state exists when  $R_0 > 1$  (solid line).

### 3. Formulation of The Delay Induced Model

Contact process between uninfected macrophage cells and parasite population is not instantaneous. Thus a delay is introduced [29] into disease transmission [24]. Then the model equations take the form as,

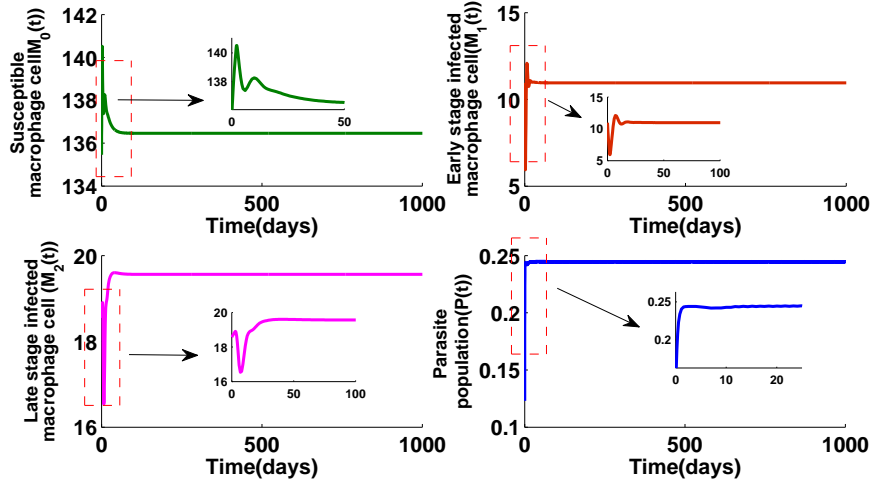


FIGURE 3. Time series solution of the model variables with delay  $\tau_1 = 2$  and  $\tau_2 = 3$ .

$$\begin{aligned}
 \frac{dM_0}{dt} &= \lambda + \delta M_1 - \sigma M_0(t - \tau_1)P(t - \tau_1)\mathbf{P}(t, \tau_1) - d_1 M_0, \\
 \frac{dM_1}{dt} &= \sigma M_0(t - \tau_1)P(t - \tau_1)\mathbf{P}(t, \tau_1) - \delta M_1 - d_2 M_1 - K_m M_1, \\
 \frac{dM_2}{dt} &= K_m M_1 - d_3 M_2, \\
 \frac{dP}{dt} &= N_m d_3 M_2 - d_4 P - \alpha P M_2.
 \end{aligned} \tag{3.1}$$

with initial conditions  $M_0(t - \tau_1) = 0$ ,  $M_1(t - \tau_1) = 0$  for  $t - \tau_1 < 0$ ,  $M_0(0) = M_{0_0}$ ,  $M_1(0) = M_{1_0}$ ,  $M_2(0) = M_{2_0}$  and  $P(0) = P_0$ . Here,  $\mathbf{P}(t, \tau_1)$  is the probability that a susceptible macrophage-cell survives  $[t - \tau_1, t)$ .

Let,  $\mathbf{P}(\zeta) = \mathbf{P}(\text{susceptible macrophage } M_0 \text{ - cell survives } [\zeta - \tau_1, \zeta))$ , then

$$\begin{aligned}
 \mathbf{P}(\zeta) &= \exp\left[-\int_{\zeta - \tau_1}^{\zeta} \left(d_1 + \frac{\sigma M_0(v - \tau_1)P(v - \tau_1)\mathbf{P}(v)}{M_0(v)}\right)dv\right] \\
 &= \exp\left[-d_1 \tau_1 - \int_{\zeta - \tau_1}^{\zeta} \left(\frac{\sigma M_0(v - \tau_1)P(v - \tau_1)\mathbf{P}(v)}{M_0(v)}\right)dv\right]
 \end{aligned}$$

and

$$\mathbf{P}(0) = \exp(-d_1 \tau_1).$$

Evidently,

$$\frac{1}{\mathbf{P}(\zeta)} \frac{d\mathbf{P}}{d\zeta} = \frac{\sigma M_0(\zeta - \tau_1) P(\zeta - \tau_1) \mathbf{P}(\zeta)}{M_0(\zeta)} - \frac{\sigma M_0(\zeta - 2\tau_1) P(\zeta - 2\tau_1) \mathbf{P}(\zeta - \tau_1)}{M_0(\zeta - \tau_1)}$$

with,

$$\mathbf{P}(0) = \exp(-d_1 \tau_1). \text{ In fact, } \mathbf{P}(\zeta) = \exp(-d_1 \tau_1) \text{ for } \zeta \leq \tau_1.$$

If the time delay is relatively small, above expressions can be approximated by the simpler [23] set of equations:

$$\begin{aligned} \frac{dM_0}{dt} &= \lambda + \delta M_1 - \sigma M_0(t - \tau_1) P(t - \tau_1) - d_1 M_0, \\ \frac{dM_1}{dt} &= \sigma M_0(t - \tau_1) P(t - \tau_1) - \delta M_1 - d_2 M_1 - K_m M_1, \\ \frac{dM_2}{dt} &= K_m M_1 - d_3 M_2, \\ \frac{dP}{dt} &= N_m d_3 M_2 - d_4 P - \alpha P M_2. \end{aligned} \tag{3.2}$$

Our model system comprises of four distinct subpopulation and the focus is to figure out the interaction mechanisms between parasite and macrophage cell. For simplicity the sandfly stage of development of the parasite is excluded and retain our model system only within the mammalian host.

In considering this aspect, in the simplest form it is assumed that the interaction among the parasite and the macrophage is not instantaneous and there exist a time delay for the infection to set in [30], [31]. Thus, delay differential equations are introduced to capture the essence of this biological phenomena. The term  $\tau_1$  is introduced, to capture the delay occurring during the mass transfer of the parasite through sandfly bite process and further  $\tau_2$  is introduced to surrogate the state change ( $K_m$ ) factor of the parasite from promastigote to amastigote stage. Incorporating this delay factor [32] in our model equation with  $\tau_1 \geq 0$  and  $\tau_2 \geq 0$  the system becomes:

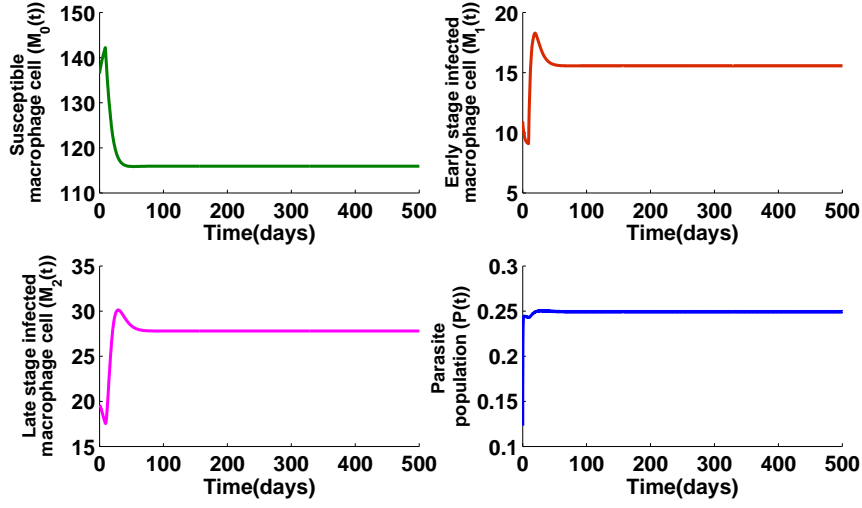


FIGURE 4. Time series solution of the model variables with delay  $\tau_1 = 9$  and  $\tau_2 = 0$ .

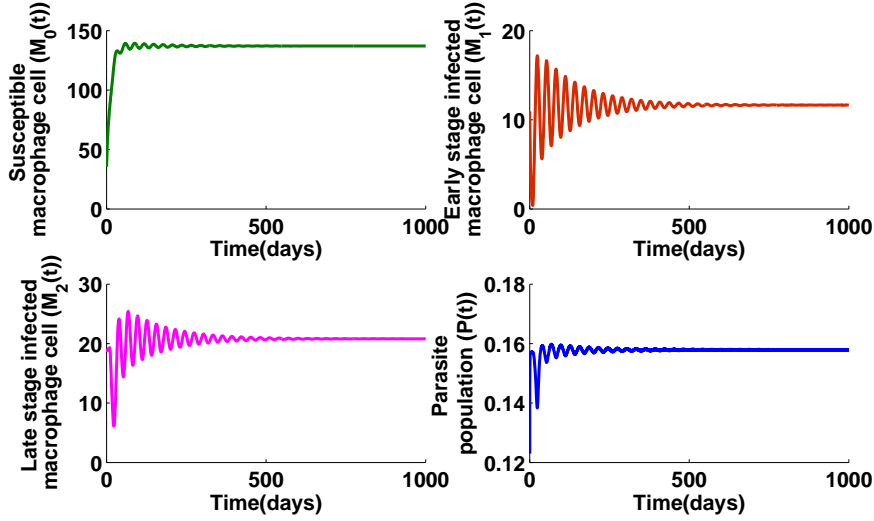


FIGURE 5. Time series solution of the model variables with delay parameter  $\tau_2 = 9.9603$ .

$$\begin{aligned}
 \frac{dM_0}{dt} &= \lambda + \delta M_1 - \sigma M_0(t - \tau_1)P(t - \tau_1) - d_1 M_0, \\
 \frac{dM_1}{dt} &= \sigma M_0(t - \tau_1)P(t - \tau_1) - \delta M_1 - d_2 M_1 - K_m M_1(t - \tau_2), \\
 \frac{dM_2}{dt} &= K_m M_1(t - \tau_2) - d_3 M_2, \\
 \frac{dP}{dt} &= N_m d_3 M_2 - d_4 P - \alpha P M_2.
 \end{aligned} \tag{3.3}$$

With the initial conditions  $M_0(\theta) \geq 0$ ,  $M_1(\theta) \geq 0$ ,  $M_2(\theta) \geq 0$ ,  $P(\theta) \geq 0$  and  $\theta \in (-\infty, 0]$ .

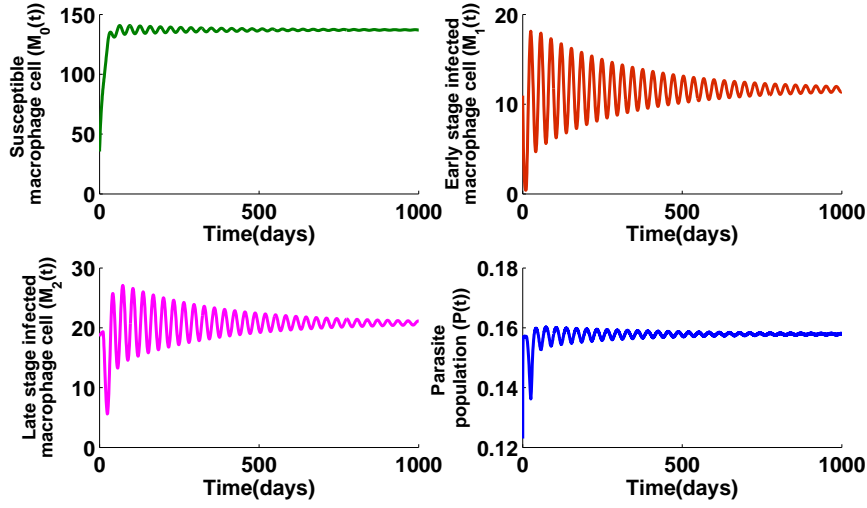


FIGURE 6. Time series solution of the model variables with delay parameter  $\tau_2 = 10.9603$ .

### 3.1. Local Stability Analysis

For local stability of the delay induced system around the interior equilibrium  $E^*$ , the system (3.3) is linearize by substituting :

$$M'_0(t) = M_0(t) - M_0(t)^*, \quad M'_1(t) = M_1(t) - M_1(t)^*,$$

$$M'_2(t) = M_2(t) - M_2(t)^* \text{ and } P'(t) = P(t) - P(t)^*.$$

The linearized form of the delay induced system at  $E^*(M_0^*, M_1^*, M_2^*, P^*)$  is stated as,

$$\begin{aligned} \frac{dM'_0}{dt} &= \delta M'_1 - \sigma M'_0(t - \tau_1)P^* - \sigma P'(t - \tau_1)M_0^* - d_1 M'_0, \\ \frac{dM'_1}{dt} &= \sigma M'_0(t - \tau_1)P^* + \sigma P'(t - \tau_1)M_0^* - \delta M'_1 - d_2 M'_1 - K_m M'_1(t - \tau_2), \\ \frac{dM'_2}{dt} &= K_m M'_1(t - \tau_2) - d_3 M'_2, \\ \frac{dP'}{dt} &= N_m d_3 M'_2 - d_4 P' - \alpha P^* M'_2 - \alpha M_2^* P'. \end{aligned} \tag{3.1.1}$$

Linearizing the system (3.3), the following jacobian matrix is obtained:

$$\begin{pmatrix} -d_1 - \sigma P^* e^{-\xi \tau_1} & \delta & 0 & -\sigma M_0^* e^{-\xi \tau_1} \\ \sigma P^* e^{-\xi \tau_1} & -d_2 - K_m e^{-\xi \tau_2} - \delta & 0 & \sigma M_0^* e^{-\xi \tau_1} \\ 0 & K_m e^{-\xi \tau_2} & -d_3 & 0 \\ 0 & 0 & N_m d_3 - \alpha P^* & -d_4 - \alpha M_2^* \end{pmatrix}.$$

The characteristic equation of the linearized system can expressed in the form as,

$$\begin{aligned} \xi^4 &+ K_1 \xi^3 + K_2 \xi^2 + K_3 \xi + K_4 + e^{-\xi \tau_1} (L_1 \xi^3 + L_2 \xi^2 + L_3 \xi + L_4) \\ &+ e^{-\xi \tau_2} (M_1 \xi^3 + M_2 \xi^2 + M_3 \xi + M_4) + e^{-\xi(\tau_1 + \tau_2)} (N_1 \xi^2 + N_2 \xi + N_3) = 0, \end{aligned} \quad (3.1.2)$$

where,

$$\begin{aligned} K_1 &= d_1 + d_2 + d_3 + d_4 + \delta + \alpha M_2^* > 0, \\ K_2 &= d_1 \delta + d_1 d_2 + d_3 \delta + d_2 d_3 + d_1 d_3 + \alpha M_2^* (d_1 + d_2 + d_3 + \delta) \\ &\quad + d_4 (d_1 + d_2 + d_3 + \delta) > 0, \\ K_3 &= d_4 (d_1 \delta + d_1 d_2 + \delta d_3 + d_2 d_3 + d_1 d_3) + d_1 d_2 d_3 + \alpha M_2^* (d_1 \delta + d_1 d_2 + \\ &\quad \delta d_3 + d_2 d_3 + d_1 d_3) + d_1 d_3 \delta > 0, \\ K_4 &= \alpha M_2^* d_1 d_2 d_3 + \alpha M_2^* d_1 d_3 \delta + d_1 d_2 d_3 d_4 + d_1 d_3 d_4 \delta > 0, \\ L_1 &= \sigma P^* > 0, \\ L_2 &= \sigma P^* d_2 + \sigma P^* d_3 + \sigma P^* \alpha M_2^* + \sigma P^* d_4 > 0, \\ L_3 &= \sigma d_2 d_4 P^* + \sigma d_2 d_3 P^* + \sigma d_3 d_4 P^* + \alpha M_2^* \sigma d_2 P^* + \alpha M_2^* \sigma d_3 P^* > 0, \\ L_4 &= \alpha M_2^* \sigma d_2 d_3 P^* + \sigma d_2 d_3 d_4 P^* > 0, \\ M_1 &= K_m > 0, \\ M_2 &= d_1 K_m + d_3 K_m + d_4 K_m + \alpha M_2^* K_m > 0, \\ M_3 &= d_1 d_4 K_m + d_3 d_4 K_m + d_1 d_3 K_m + \alpha M_2^* d_1 K_m + \alpha M_2^* d_3 K_m > 0, \\ M_4 &= \alpha M_2^* d_1 d_3 K_m + d_1 d_3 d_4 K_m > 0, \\ N_1 &= \sigma K_m P^* > 0, \\ N_2 &= \sigma K_m P^* d_3 + \sigma K_m P^* d_4 + \sigma K_m P^* \alpha M_2^* + \alpha P^* M_0^* \sigma K_m - N_m d_3 \sigma M_0^* K_m, \\ N_3 &= d_1 \alpha P^* M_0^* \sigma K_m + \alpha M_2^* \sigma K_m d_3 P^* + \sigma d_3 d_4 K_m P^* - d_1 N_m d_3 \sigma M_0^* K_m. \end{aligned} \quad (3.1.3)$$

The characteristic equation (3.1.2) is a transcendental equation in  $\xi$  and it has infinitely many roots. It is to be noted that if all the roots of the characteristic equation have negative real parts then  $E^*$  is locally asymptotically stable and otherwise unstable. The following cases are considered for describing the stability analysis.

**Case 1:**  $\tau_1 = 0$  and  $\tau_2 = 0$ ,

in this case both the delays are absent. The characteristics equation (3.1.2) becomes,

$$\begin{aligned} \xi^4 + \xi^3(K_1 + L_1 + M_1) + \xi^2(K_2 + L_2 + M_2 + N_1) + \xi(K_3 + L_3 + M_3 + N_2) + \\ (K_4 + L_4 + M_4 + N_3) = 0. \end{aligned} \quad (3.1.4)$$

From the Routh-Hurwitz criterion, the necessary and sufficient condition for locally asymptotically stable are,

$$(i) (K_1 + L_1 + M_1)(K_2 + L_2 + M_2 + N_1) > (K_3 + L_3 + M_3 + N_2) \text{ and}$$

$$(ii) (K_1 + L_1 + M_1)(K_2 + L_2 + M_2 + N_1)(K_3 + L_3 + M_3 + N_2) > (K_1 + L_1 + M_1)^2(K_4 + L_4 + M_4 + N_3) + (K_3 + L_3 + M_3 + N_2)^2.$$

This is equivalent to the condition as in the non-delayed system analysis.

**Case 2:**  $\tau_1 > 0$  and  $\tau_2 = 0$ .

If there is no time delay for transmission from promastigote to amastigote stage i.e.,  $\tau_2 = 0$ , then the characteristic equation (3.1.2) takes the form,

$$\begin{aligned} \xi^4 + \xi^3(K_1 + M_1) + \xi^2(K_2 + M_2) + \xi(K_3 + M_3) + (K_4 + M_4) \\ + e^{-\xi\tau_1}[L_1\xi^3 + (L_2 + N_1)\xi^2 + (L_3 + N_2)\xi + (L_4 + N_3)] = 0. \end{aligned} \quad (3.1.5)$$

For  $\tau_1 > 0$ , equation (3.1.2) is a transcendental equation. Let  $\xi = i\omega$  be a root of equation (3.1.2) and equating real and imaginary parts the following result can be obtained,

$$\begin{aligned} \omega^4 - \omega^2(K_2 + M_2) + (K_4 + M_4) &= \cos \omega \tau_1 [\omega^2(L_2 + N_1) - (L_4 + N_3)] \\ + \sin \omega \tau_1 [\omega^3 L_1 - \omega(L_3 + N_2)], \end{aligned} \quad (3.1.6)$$

$$\begin{aligned} \omega(K_3 + M_3) - \omega^3(K_1 + M_1) &= \cos \omega \tau_1 [\omega^3 L_1 - \omega(L_3 + N_2)] \\ - \sin \omega \tau_1 [\omega^2(L_2 + N_1) - (L_4 + N_3)]. \end{aligned}$$

Squaring and adding above two equations, the following equation is obtained,

$$\begin{aligned} \omega^8 + \omega^6[(K_1 + M_1)^2 - 2(K_2 + M_2) - L_1^2] + \omega^4[(K_2 + M_2)^2 + 2(K_4 + M_4) \\ - 2(K_3 + M_3)(K_1 + M_1) - (L_2 + N_1)^2 + 2N_1(L_3 + N_2)] \\ + \omega^2[(K_3 + M_3)^2 - 2(K_2 + M_2)(K_4 + M_4) + 2(L_2 + N_1)(L_4 + N_3) - (L_3 + N_2)^2] \\ + [(K_4 + M_4)^2 - (L_4 + N_3)^2] = 0. \end{aligned} \quad (3.1.7)$$

Substituting  $\omega^2 = \rho$  in the equation (3.1.7), the following equation is obtained,

$$\rho^4 + b_1 \rho^3 + b_2 \rho^2 + b_3 \rho + b_4 = 0, \quad (3.1.8)$$

where,

$$\begin{aligned} b_1 &= (K_1 + M_1)^2 - 2(K_2 + M_2) - L_1^2, \\ b_2 &= (K_2 + M_2)^2 + 2(K_4 + M_4) - 2(K_3 + M_3)(K_1 + M_1) - (L_2 + N_1)^2 + 2N_1(L_3 + N_2), \\ b_3 &= (K_3 + M_3)^2 - 2(K_2 + M_2)(K_4 + M_4) + 2(L_2 + N_1)(L_4 + N_3) - (L_3 + N_2)^2, \\ b_4 &= (K_4 + M_4)^2 - (L_4 + N_3)^2. \end{aligned}$$

In the delay induced system (3.3), the infected steady state  $E^*$  will be locally asymptotically stable for all  $\tau_1 > 0$ , if  $b_1 > 0, b_4 > 0, b_1 b_2 > b_3$  and  $b_1(b_2 b_3 - b_1 b_4) > b_3^2$  the condition (Routh-Hurwitz) is satisfied.



**Case 3:**  $\tau_1 = 0$  and  $\tau_2 > 0$ ,

If there is no time delay for susceptible macrophage and parasite interaction i.e.,  $\tau_1$  is not present in that term, the characteristic equation (3.1.2) becomes,

$$\begin{aligned} &\xi^4 + \xi^3(K_1 + L_1) + \xi^2(K_2 + L_2) + \xi(K_3 + L_3) + (K_4 + L_4) \\ &+ e^{-\xi\tau_2}[M_1\xi^3 + (M_2 + N_1)\xi^2 + (M_3 + N_2)\xi + (M_4 + N_3)] = 0. \end{aligned} \quad (3.1.9)$$

Again, if  $\xi = i\omega$  is substituted, then

$$\begin{aligned} &\omega^4 - \omega^2(K_2 + L_2) + (K_4 + L_4) = \cos \omega\tau_2[\omega^2(M_2 + N_1) - (M_4 + N_3)] \\ &+ \sin \omega\tau_2[\omega^3M_1 - \omega(M_3 + N_2)] \end{aligned} \quad (3.1.10)$$

and

$$\begin{aligned} &\omega(K_3 + L_3) - \omega^3(K_1 + L_1) = \cos \omega\tau_2[\omega^3M_1 - \omega(M_3 + N_2)] \\ &- \sin \omega\tau_2[\omega^2(M_2 + N_1) - (M_4 + N_3)]. \end{aligned} \quad (3.1.11)$$

Squaring and adding above two equations and then substituting  $\omega^2 = \beta$ , the following can be obtained,

$$\beta^4 + c_1\beta^3 + c_2\beta^2 + c_3\beta + c_4 = 0, \quad (3.1.12)$$

where,

$$\begin{aligned} c_1 &= (K_1 + L_1)^2 - 2(K_2 + L_2) - M_1^2, \\ c_2 &= (K_2 + L_2)^2 + 2(K_4 + L_4) - 2(K_3 + L_3)(K_1 + L_1) - (M_2 + N_1)^2 + 2M_1(M_3 + N_2), \\ c_3 &= (K_3 + L_3)^2 - 2(K_2 + L_2)(K_4 + L_4) + 2(M_2 + N_1)(M_4 + N_3) - (M_3 + N_2)^2, \\ c_4 &= (K_4 + L_4)^2 - (M_4 + N_3)^2. \end{aligned}$$

From the above analysis, the following Corollaries can be obtained:

**Corollary 3.1.1.** *In a delay induced system (3.3), the infected steady state  $E^*$  will be locally asymptotically stable for all  $\tau_2 > 0$ , if the following conditions are satisfied,  $c_1 > 0, c_4 > 0, c_1 c_2 > c_3$  and  $c_1(c_2 c_3 - c_1 c_4) > c_3^2$ .*

**Corollary 3.1.2.** *If  $c_4 < 0$ , then equation (3.1.12) has at least one positive root.*

If  $\omega_0$  be a positive root of (3.1.12), then equation (3.1.9) will have a purely imaginary root  $\pm i\omega_0$  corresponding to  $\tau_2$ . For stability of the delay induced system (3.3), the critical value of  $\tau_2$  can be estimated. Now, from equation (3.1.10) and equation (3.1.11), the following expression is obtained:

$$\tau_2^* = \frac{1}{\omega_0} \arccos \left[ \frac{\{\omega_0^2(M_2 + N_1) - (M_4 + N_3)\} \{\omega_0^4 - \omega_0^2(K_2 + L_2) + (K_4 + L_4)\}}{\Omega_0} + \frac{\{\omega_0^3 M_1 - \omega_0(M_3 + N_2)\} \{\omega_0(K_3 + L_3) - \omega_0^3(K_1 + L_1)\}}{\Omega_0} \right],$$

where,

$$\Omega_0 = \{\omega_0^2(M_2 + N_1) - (M_4 + N_3)\}^2 + \{\omega_0^3 M_1 - \omega_0(M_3 + N_2)\}^2.$$

Results from the above analysis can be written as a theorem.

**Theorem 3.1.1.** *If  $c_4 < 0$  is satisfied, then the steady state  $E^*$  is locally asymptotically stable for  $\tau_2 < \tau_2^*$  and becomes unstable for  $\tau_2 > \tau_2^*$ . When  $\tau_2 = \tau_2^*$ , then Hopf-bifurcation occurs.*

**Proof.**

See Appendix-A.

**Case 4:**  $\tau_1 > 0$  and  $\tau_2 > 0$ ,

If all the roots of equation (3.1.9) have negative real parts for  $\tau_2 > 0$  then the system is locally asymptotically stable. There exists a  $\tau_1^*$  depending upon  $\tau_2$  such that all roots of equation (3.1.2) have negative real parts, whenever  $\tau_1 < \tau_1^*$ .

#### 4. The Optimal Control Problem

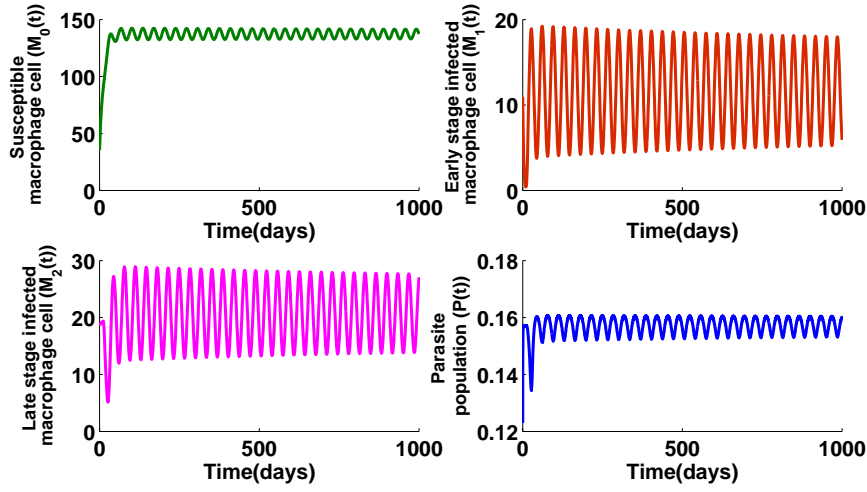


FIGURE 7. Time series solution of the model variables with delay parameter  $\tau_2 = 11.9603$ .

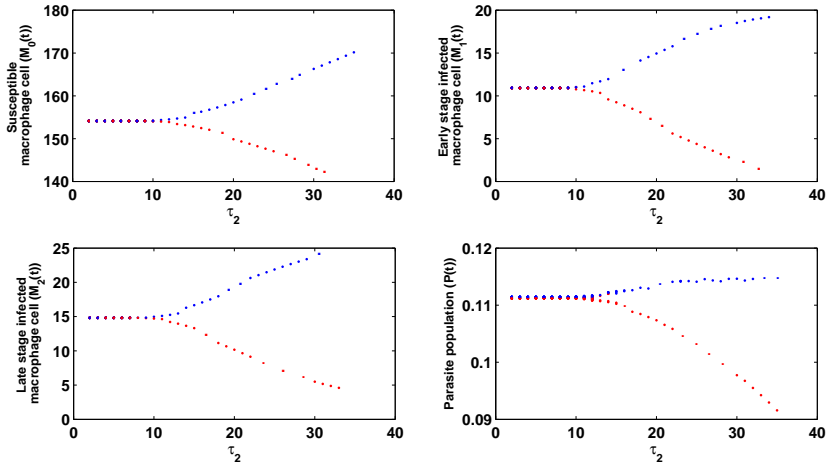


FIGURE 8. Bifurcation diagram of all four species for varying  $\tau_2$  and other parameters fixed as given in Table 1.

The aim is to reduce the rate of infection by introducing drug into the delayed system (3.3). Here,  $u(t)$  is considered as the surrogate of proper drug dose applied in the delayed system. It is very clear that, interaction between macrophage and parasite there is a possibility of infection. Thus uninfected macrophage is invaded by promastigote stage and also promastigote stage transformed into amastigote stage by state change ( $K_m$ ). It facilitates to generate the infected macrophage cell population that manifested the disease Leishmaniasis. Thus, in this circumstance, the infected macrophage cells by applying suitable drug. The control parameter

**Table 1.** List of parameters used in the models simulation.

Parameter	Definition	Range	Value	Reference
$\lambda$	Source constant of susceptible macrophage	$10 - 18 \text{ mm}^3 \text{ day}^{-1}$	10	[28]
$\delta$	Rate constant of change of macrophage state	$0.11 - 0.36 \text{ day}^{-1}$	0.35	[28]
$\sigma$	Rate constant for infectivity	$0.11 - 0.23 \text{ day}^{-1}$	0.21	<i>Estimated</i>
$d_1$	Death rate of susceptible macrophage	$0.015 - 0.17 \text{ day}^{-1}$	0.16	[28]
$K_m$	State change rate from (from promastigote to amastigote stage)	$0.12 - 0.27 \text{ day}^{-1}$	0.25	[28]
$d_2$	Death rate of early stage infected macrophage cell	$0.02 - 0.09 \text{ day}^{-1}$	0.04	[28]
$d_3$	Death rate of late stage infected macrophage cell	$0.10 - 0.14 \text{ day}^{-1}$	0.14	[28]
$d_4$	Death rate of parasite population	$0.20 - 0.29 \text{ day}^{-1}$	0.20	[28]
$N_m$	Burst size	$0.18 - 0.28 \text{ mm}^3 \text{ day}^{-1}$	0.18	<i>Estimated</i>
$\alpha$	Loss of parasite population	$0.02 - 0.16 \text{ days}$	0.15	[28]

$(1 - u(t))$  is introduced in the dynamical model system (3.3). Thus, for  $t_0 \leq t \leq t_f$ , the state system reduces to:

$$\begin{aligned}
\frac{dM_0}{dt} &= \lambda + \delta M_1 - (1 - u(t))\sigma M_0(t - \tau_1)P(t - \tau_1) - d_1 M_0, \\
\frac{dM_1}{dt} &= \sigma M_0(t - \tau_1)P(t - \tau_1)(1 - u(t)) - \delta M_1 - d_2 M_1 - (1 - u(t))K_m M_1(t - \tau_2), \\
\frac{dM_2}{dt} &= (1 - u(t))K_m M_1(t - \tau_2) - d_3 M_2, \\
\frac{dP}{dt} &= N_m d_3 M_2 - d_4 P - \alpha P M_2.
\end{aligned} \tag{4.1}$$

Where  $M_0(0), M_1(0), M_2(0)$  and  $P(0)$  are the initial conditions.

The control input  $u(t)$  lies between 0 and 1. Also  $u(t) = 1$  represents the maximum use of drug and  $u(t) = 0$ , which represents no use of drug. Since control reduces the infected macrophage cell population and increase the healthy macrophage cell population so the parasite population automatically be controlled.

The objective function can be defined as:

$$J(u) = \int_{t_0}^{t_f} [M_1(t) - M_0(t) + W(u(t))^2] dt. \quad (4.2)$$

Optimal control approach is used to minimize the infected macrophage cells as well as to maximize uninfected macrophage cells [33]. The parameter  $W(\geq 0)$  considered as a preferred ‘weight’ for the cost-benefit function. The aim is to figure out the optimal profile of  $u(t)$  i.e.  $u^*(t)$  for which the cost function,  $J(u^*)$  is minimum. ‘Pontryagin’s Minimum Principle’ is used to solve the delay induced optimal control problem [34].

For solving the problem, Hamiltonian  $H$  is written as,

$$\begin{aligned} H = & M_1(t) - M_0(t) + W(u(t))^2 + \rho_1[\lambda + \delta M_1 - (1 - u(t))\sigma M_0(t - \tau_1)P(t - \tau_1) - d_1 M_0] \\ & + \rho_2[(1 - u(t))\sigma M_0(t - \tau_1)P(t - \tau_1) - \delta M_1 - d_2 M_1 - (1 - u(t))K_m M_1(t - \tau_2)] \\ & + \rho_3[(1 - u(t))K_m M_1(t - \tau_2) - d_3 M_2] + \rho_4[N_m d_3 M_2 - d_4 P - \alpha P M_2] \\ & + v_1 u(t) + v_2(1 - u(t)), \end{aligned} \quad (4.3)$$

where  $\rho_1, \rho_2, \rho_3$  and  $\rho_4$  are regarded as adjoint variables and  $v_1, v_2$  are considered as penalty multipliers subject to the condition,

$$u = 0, \text{ where } v_1 \neq 0 \text{ and } v_2 = 0$$

$$u = 1, \text{ where } v_1 = 0 \text{ and } v_2 \neq 0.$$

The corresponding adjoint equations are given by:

$$\begin{aligned} \frac{d\rho_1}{dt} &= -\frac{\partial H}{\partial M_0} - \chi_{[0, t_f - \tau_1]}(t) \frac{\partial H}{\partial M_0 \tau_1}(t + \tau_1), \quad \frac{d\rho_2}{dt} = -\frac{\partial H}{\partial M_1} - \chi_{[0, t_f - \tau_2]}(t) \frac{\partial H}{\partial M_1 \tau_2}(t + \tau_2), \\ \frac{d\rho_3}{dt} &= -\frac{\partial H}{\partial M_2}, \quad \frac{d\rho_4}{dt} = -\frac{\partial H}{\partial P} - \chi_{[0, t_f - \tau_1]}(t) \frac{\partial H}{\partial P \tau_1}(t + \tau_1). \end{aligned} \quad (4.4)$$

From above relations, the following adjoint system can be deduced,

$$\begin{aligned} \frac{d\rho_1}{dt} &= -[-1 - \rho_1 d_1 + \rho_1(t + \tau_1)\sigma P(t - \tau_1)\chi_{[0, t_f - \tau_1]}(t)\{u(t + \tau_1) - 1\} \\ &\quad - \rho_2(t + \tau_1)\sigma P(t - \tau_1)\chi_{[0, t_f - \tau_1]}(t)\{u(t + \tau_1) - 1\}], \\ \frac{d\rho_2}{dt} &= -[1 + \rho_1 \delta - \rho_2(\delta + d_2) - (\rho_3(t + \tau_2) - \rho_2(t + \tau_2))K_m \chi_{[0, t_f - \tau_2]}(t)\{u(t + \tau_2) - 1\}], \\ \frac{d\rho_3}{dt} &= -[-\rho_3 d_3 + \rho_4(N_m d_3 - \alpha P)], \end{aligned}$$

$$\begin{aligned} \frac{d\rho_4}{dt} = & -[\rho_1(t + \tau_1)\sigma M_0(t - \tau_1)\chi_{[0,t_f-\tau_1]}(t)\{u(t + \tau_1) - 1\} \\ & - \rho_2(t + \tau_1)\sigma M_0(t - \tau_1)\chi_{[0,t_f-\tau_1]}(t)\{u(t + \tau_1) - 1\} - \rho_4(d_4 + \alpha M_2)]. \end{aligned} \quad (4.5)$$

Using Pontryagin minimum principle with delay, the boundary conditions for adjoint system as  $\rho_i(t_f) = 0$ .

Again  $H$  can be written in the form as,

$$\begin{aligned} H = & W(u(t))^2 - \rho_1(1 - u(t))\sigma M_0(t - \tau_1)P(t - \tau_1) + \rho_2(1 - u(t))\sigma M_0(t - \tau_1)P(t - \tau_1) \\ & + (1 - u(t))(\rho_3 - \rho_2)K_m M_1(t - \tau_2) + v_1 u(t) + v_2(1 - u(t)) + \text{terms without } u, \end{aligned}$$

Now, differentiating  $H$  with respect to  $u$ , the following relation is obtained,

$$\begin{aligned} \frac{\partial H}{\partial u} = & 2Wu(t) + \rho_1\sigma M_0(t - \tau_1)P(t - \tau_1) - \rho_2\sigma M_0(t - \tau_1)P(t - \tau_1) \\ & + (\rho_2 - \rho_3)K_m M_1(t - \tau_2) + v_1 - v_2. \end{aligned}$$

This expression should be equal to zero at  $u^*(t)$ .

Thus,

$$\begin{aligned} 2Wu^*(t) + \rho_1\sigma M_0(t - \tau_1)P(t - \tau_1) - \rho_2\sigma M_0(t - \tau_1)P(t - \tau_1) \\ + K_m(\rho_2 - \rho_3)M_1(t - \tau_2) + v_1 - v_2 = 0. \end{aligned}$$

Solving for the optimal control yields,

$$u^*(t) = \frac{\sigma(\rho_2 - \rho_1)M_0(t - \tau_1)P(t - \tau_1) + (\rho_3 - \rho_2)K_m M_1(t - \tau_2) + v_2 - v_1}{2W}. \quad (4.6)$$

There are three cases to be considered.

Case 1:  $0 < u^*(t) < 1$ ,

Case 2:  $u^*(t) = 0$ ,

Case 3:  $u^*(t) = 1$ .

Case 1:  $0 < u^*(t) < 1$ , subject to the condition  $v_1 = v_2 = 0$ ,

$$u^*(t) = \frac{\sigma(\rho_2 - \rho_1)M_0(t - \tau_1)P(t - \tau_1) + (\rho_3 - \rho_2)K_m M_1(t - \tau_2)}{2W}.$$

Case 2:  $u^*(t) = 0$ , subject to the condition  $v_1 \neq 0$  and  $v_2 = 0$ ,

$$\sigma(\rho_2 - \rho_1)M_0(t - \tau_1)P(t - \tau_1) + (\rho_3 - \rho_2)K_m M_1(t - \tau_2) = v_1.$$

Case 3:  $u^*(t) = 1$ , subject to the condition  $v_1 = 0$  and  $v_2 \neq 0$ ,

$$\sigma(\rho_2 - \rho_1)M_0(t - \tau_1)P(t - \tau_1) + (\rho_3 - \rho_2)K_m M_1(t - \tau_2) + v_2 = 2W.$$

Therefore, the compact form of the optimal  $u(t)$ , i.e.  $u^*(t)$  can be stated below:

$$u^*(t) = \max\left(\min\left(\frac{\sigma(\rho_2 - \rho_1)M_0(t - \tau_1)P(t - \tau_1) + (\rho_3 - \rho_2)K_m M_1(t - \tau_2)}{2W}, 1\right), 0\right). \quad (4.7)$$

Above results are represented by the following theorem:

**Theorem 4.1.** *If the objective cost function  $J(u^*(t))$  is minimum for the optimal control  $u^*(t)$  corresponding to the interior equilibrium  $(M_0^*, M_1^*, M_2^*, P^*)$  then there exist adjoint variables  $\rho_1, \rho_2, \rho_3$ , and  $\rho_4$  which satisfy the following system of equations:*

$$\begin{aligned} \frac{d\rho_1}{dt} &= -[-1 - \rho_1 d_1 + \rho_1(t + \tau_1)\sigma P(t - \tau_1)\chi_{[0, t_f - \tau_1]}(t)\{u(t + \tau_1) - 1\} \\ &\quad - \rho_2(t + \tau_1)\sigma P(t - \tau_1)\chi_{[0, t_f - \tau_1]}(t)\{u(t + \tau_1) - 1\}], \\ \frac{d\rho_2}{dt} &= -[1 + \rho_1 \delta - \rho_2(\delta + d_2) - (\rho_3(t + \tau_2) - \rho_2(t + \tau_2))K_m \chi_{[0, t_f - \tau_2]}(t)\{u(t + \tau_2) - 1\}], \\ \frac{d\rho_3}{dt} &= -[-\rho_3 d_3 + \rho_4(N_m d_3 - \alpha P)], \\ \frac{d\rho_4}{dt} &= -[\rho_1(t + \tau_1)\sigma M_0(t - \tau_1)\chi_{[0, t_f - \tau_1]}(t)\{u(t + \tau_1) - 1\} \\ &\quad - \rho_2(t + \tau_1)\sigma M_0(t - \tau_1)\chi_{[0, t_f - \tau_1]}(t)\{u(t + \tau_1) - 1\} - \rho_4(d_4 + \alpha M_2)]. \end{aligned}$$

with the transversality condition satisfying  $\rho_i(t_f) = 0$  ( $i = 1, 2, 3, 4$ ).

Moreover, the optimal control is given by:

$$u^*(t) = \max\left(\min\left(\frac{\sigma(\rho_2 - \rho_1)M_0(t - \tau_1)P(t - \tau_1) + (\rho_3 - \rho_2)K_m M_1(t - \tau_2)}{2W}, 1\right), 0\right).$$

The analytical results of optimal control are fulfilled by numerical simulation using MATLAB. Forward and backward difference approximation algorithms is used to solve the optimal control problem [34].

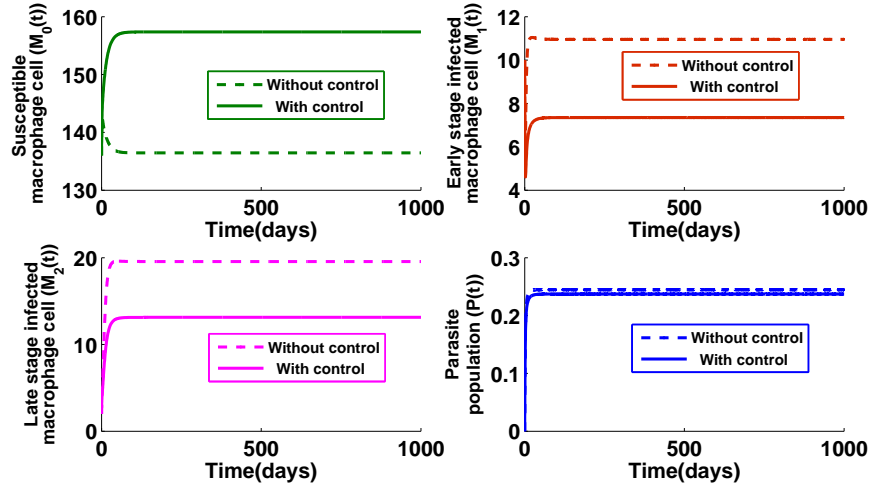


FIGURE 9. Time series solution of the model variables without control and with control ( $u = 0.4$ ) for infected state.

## 5. Numerical Simulation

Numerical simulation of the model (2.1) is done with the basic model parameter values as prescribed in Table 1. From the existence and stability analysis of the non-delayed and delayed system,  $K_m$  seems to be an important parameter. Here, unit of  $\tau_1$  and  $\tau_2$  is *day*.

Figure 1 shows the contour plot of the basic reproductive ratio ( $R_0$ ) function of  $K_m$  and  $N_m$ . From this plot it is observed that if  $K_m$  and  $N_m$  are small, then  $R_0$  can be below unity. But if  $K_m$  and  $N_m$  are both very large, then  $R_0$  exceed 1.

Figure 2 it is clearly observed that when state change rate (from promastigote to amastigote) is below its threshold value ( $K_m < 0.25$ ), the system attains its infection free state. But if the state change rate ( $K_m > 0.25$ ), the system moves to its infected state and the disease persists.

The effects of delay are exhibited from Figure 3 to Figure 7. In Figure 3, simulate result of the system shows for parametric condition ( $\tau_1 = 2$ )  $> 0$  and ( $\tau_2 = 3$ )  $> 0$ . Furthermore, from Figure



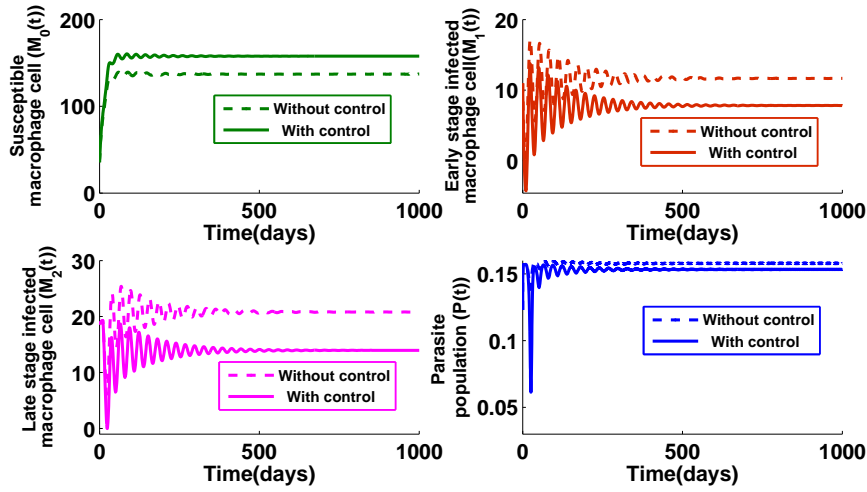


FIGURE 10. Behaviour of the delayed system without drug and with drug for  $\tau_2 = 9.9603$ .

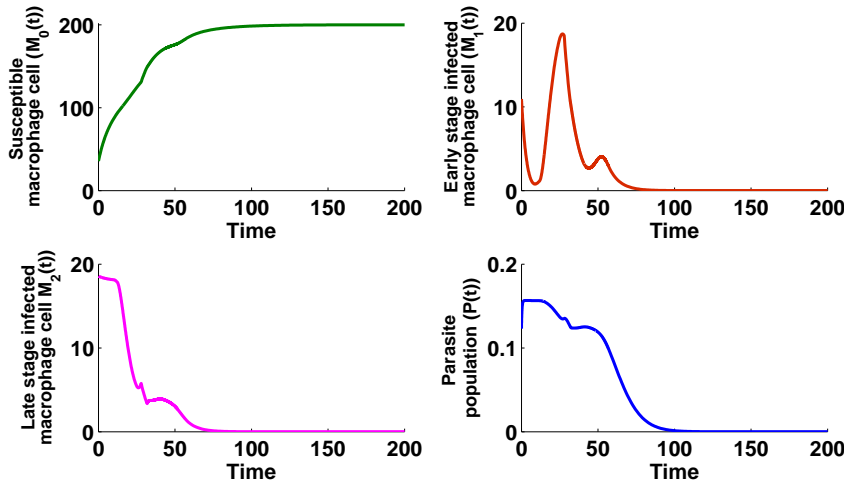


FIGURE 11. The behavior of the delayed system with optimal control schedule of the drug therapy for  $\tau_2 = 9.9603$ .

4, scenarios is described for  $\tau_1 = 9$  and  $\tau_2 = 0$ . In Figure 5,  $\tau_1 = 0$  and  $\tau_2 = 9.9603$  and in Figure 6,  $\tau_1 = 0$  and  $\tau_2 = 10.9603$  and in Figure 7,  $\tau_1 = 0$   $\tau_2 = 11.9603$ . Results are reflected in figures. It is observed that oscillation in the system dynamics increases with increasing value of delay parameter ( $\tau_2$ ). To see the delay effect in the disease dynamics, three values of  $\tau_2$  are taken keeping  $\tau_1$  as fixed.

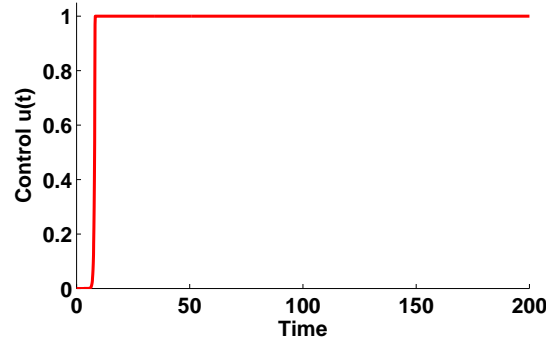


FIGURE 12. Optimal schedule of the drug therapy is plotted as function of time.

Bifurcation diagram is shown in Figure 8 using  $K_m = 0.19$  and  $N_m = 0.13$ . It is also observed that as  $\tau_2$  increases beyond the critical value, ( $\tau_2 = 11.9603$ ), the system enters into a chaotic situation. Comparison of the system behavior is shown for two cases, Case-I: without control and Case-II: with control and depicted in Figure 9 with the value of the control variable as  $u = 0$  and  $u(t) = 0.4$  respectively. Moreover, the cases are considered for delayed system and presented in Figure 10 with same values of control parameter value as  $u = 0.4$  and  $\tau_2 = 9.9603$  day.

The behavior of the delayed system in presence of optimal control is shown in Figure 11 and Figure 12. From these figures, it is observed that the susceptible macrophage cell population increases whereas the rest of populations decreases with time as desired.

## 6. Discussion

In this research article, a mathematical model is formulated for leishmaniasis consisting four populations which are interrelated to the transmission of the disease cutaneous leishmaniasis. Analytical studies indicates the infection free steady state in the absence of delay exists if  $R_0 < 1$ . On the other hand, when  $R_0 > 1$ , the infection free state loses its stability and the system tends towards the infected situation. It is clear that susceptible macrophage cell population is

decreased in 40 days (approx.) and infected macrophage cell population is gradually increased in before 35 days.

Analytical and numerical results reveal that a time delay in the disease transmission term may cause the non-trivial equilibrium  $E^*$  to become unstable as the time delay increases and the threshold condition is obtained for this un-stability. As the time delay increases further, the non-trivial equilibrium is again unstable. The threshold value of delay is also obtained for which the system is locally asymptotically stable or unstable. Also the system around the endemic equilibrium  $E^*$  as  $\tau_2$  overshoots the critical value  $\tau_2^*$ . When, optimal control strategy is introduced in the proposed model system (2.1), susceptible macrophage cell population reaches up to 155 cells/mm<sup>3</sup>(approx.). Also, control in the delay induced system (3.3) is incorporated. When the delay  $\tau_2 = 9.9603$  in the state change term then susceptible macrophage cell population reaches up to 160 cells/mm<sup>3</sup>(approx.). Moreover, if optimal control approach is used, susceptible macrophage cell population becomes stable more rapidly with respect to time rather than delayed system with control. It can be observed that significant number of susceptible or healthy macrophage cell population will be increased. On the contrary, a considerable decrease in the infected cell population will occur. This imply that optimal control approach will help in designing an innovative cost-effective safe therapeutic arena.

## 7. Conclusion

The effect of delay on uninfected macrophage cell, infected macrophage cell and parasite population is highlighted. The pathogenesis of the disease is reduced by giving control on the disease transmission. The intention is to observe the dynamical system for evaluating the impact of state change from promastigote to amastigote stage and release parasite into the tissue in the mammalian cycle of disease. Special emphasis is focused on updated observations to explain the new prospect on the disease leishmaniasis. From optimal control strategy one can achieve healthy macrophage cell population more quickly rather than fixed control approach with respect to state change parameter ( $K_m$ ). Thus, adoption of optimal control strategy is truly acceptable in terms of enhancing the life perspective of human and mitigating the problem of

this well known neglected tropical disease.

### **Conflict of Interests**

The authors declare that there is no conflict of interests.

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## Appendix-A

To show that at  $\tau_2 = \tau_2^*$  there exist a Hopf-bifurcation, we need to verify the transversal condition  $\left. \frac{d}{d\tau} \left( \text{Re} \xi(\tau_2) \right) \right|_{\tau_2 = \tau_2^*}$ . By differentiation (3.1.9) with respect to  $\tau_2$ , we get,

$$\begin{aligned} & (4\xi^3 + 3K_1\xi^2 + 2K_2\xi + K_3 + 3L_1\xi^2 + 2L_2\xi + L_3) \frac{d\xi}{d\tau_2} \\ & + \left[ e^{-\xi\tau_2} (3M_1\xi^2 + 2M_2\xi + M_3 + 2N_1\xi + N_2) \right. \\ & \left. - \tau_2 e^{-\xi\tau_2} (M_1\xi^3 + M_2\xi^2 + M_3\xi + M_4 + N_1\xi^2 + N_2\xi + N_3) \right] \frac{d\xi}{d\tau_2} \\ & = \xi e^{-\xi\tau_2} (M_1\xi^3 + M_2\xi^2 + M_3\xi + M_4 + N_1\xi^2 + N_2\xi + N_3). \end{aligned}$$

From (3.1.12) we have the relation,

$$\begin{aligned} \left( \frac{d\xi}{d\tau_2} \right)^{-1} &= \frac{3\xi^4 + 2K_1\xi^3 + K_2\xi^2 + 2L_1\xi^3 + L_2\xi^2 - (K_4 + L_4)}{-\xi^2(\xi^4 + K_1\xi^3 + K_2\xi^2 + K_3\xi + K_4 + L_1\xi^3 + L_2\xi^2 + L_3\xi + L_4)} \\ &+ \frac{2M_1\xi^3 + M_2\xi^2 + N_1\xi^2 - (M_4 + N_3)}{\xi^2(M_1\xi^3 + M_2\xi^2 + M_3\xi + M_4 + N_1\xi^2 + N_2\xi + N_3)} - \frac{\tau_2}{\xi}, \end{aligned}$$

Thus,

$$\begin{aligned} & \text{Sign} \left\{ \frac{d(\text{Re} \xi)}{d\tau_2} \right\}_{\xi = i\omega_0} = \text{Sign} \left\{ \text{Re} \left( \frac{d\xi}{d\tau_2} \right)^{-1} \right\}_{\xi = i\omega_0} \\ & = \text{Sign} \left\{ \text{Re} \left[ \frac{3\xi^4 + 2K_1\xi^3 + K_2\xi^2 + 2L_1\xi^3 + L_2\xi^2 - (K_4 + L_4)}{-\xi^2(\xi^4 + K_1\xi^3 + K_2\xi^2 + K_3\xi + K_4 + L_1\xi^3 + L_2\xi^2 + L_3\xi + L_4)} \right]_{\xi = i\omega_0} \right. \\ & \left. + \text{Re} \left[ \frac{2M_1\xi^3 + M_2\xi^2 + N_1\xi^2 - (M_4 + N_3)}{\xi^2(M_1\xi^3 + M_2\xi^2 + M_3\xi + M_4 + N_1\xi^2 + N_2\xi + N_3)} \right]_{\xi = i\omega_0} \right\}. \end{aligned}$$

Since  $\omega_0$  is the largest positive root of (3.1.9), we have  $\left. \frac{d}{d\tau} \left( \text{Re} \xi(\tau_2) \right) \right|_{\tau_2 = \tau_2^*} > 0$ . Again for  $\tau_2 > \tau_2^*$  the real part of  $\xi(\tau_2)$  becomes positive and thus the system  $E^*$  becomes unstable.