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IMPULSIVE APPLICATION TO DESIGN EFFECTIVE THERAPIES AGAINST CUTANEOUS LEISHMANIASIS UNDER MATHEMATICAL PERCEPTIVE

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Abstract. Leishmaniasis is one type of infectious diseases that is generated by different parasites of the Leishmania. The disease spreads in mammals (both human and animal hosts) through the bites of various infected sand fly. species. Leishmania parasites have two important developmental stages in their life cycle such as Promastigote (the proliferative form found in the lumen of the female sand fly) and another one is Amastigote (the proliferative form found inside several types of mammalian host cells). Here we have considered a mathematical model consisting susceptible (uninfected) macrophage cell, early stage infected macrophage cell (Promastigote), late stage infected macrophage cell (Amastigote) and parasite population. We have applied drugs like Sodium Stibogluconate and Meglumine Antimoniate for reducing parasite population in impulsive way under mathematical framework. Our analytical and numerical results justify that controlling parasite population by applying drugs in impulsive way gives realistic outcome. Also we have established the efficiency of the drug dose that contributes a greater effect on the system moving towards the healthy situation.

Keywords: Cutaneous Leishmaniasis (CL); macrophage; promastigote; amastigote; impulsive approach.

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1. Introduction

Leishmaniasis is a special type of diverse and complex vector borne diseases, which is caused by intercellular protozoan parasite of the *Leishmania genus*. The disease is transmitted by the bite of infected female *Phlebotomous papatasi* sand flies [1, 2]. Presently the disease is endemic in more or less eighty eight countries. Mostly affected countries are Afghanistan, Algeria, Iran, Iraq, Pakistan, Brazil and Peru that include more than ninety percent cases of the world. There are approximated 12 million cases worldwide with 1.5 to 2 million fresh cases in every year [3, 4]. There are generally four clinical prototypes for leishmaniasis and these are characterized as Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (known as Espundia), Visceral Leishmaniasis (known as Kala-azar) and Post Kala-azar Dermal Leishmaniasis (PKDL). The disease has four eco-epidemiological units such as zoonotic and anthroponotic cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) respectively. In anthroponotic form, human are only responsible for infection. Otherwise in zoonotic cycles, animals are reservoirs, which carry the leishmania parasites [5, 6].

The infected female sand fly pushes the parasite's motile and flagellated stage into the human skin (termed as Promastigote). After entering the leishmania parasite into the human body, it's intention is to attack and reside in the macrophage tissues. Once the parasite enters into the human host, it is phagocytosed by macrophages and then becomes Amastigote in nature. The Amastigote form is then able to infect additional macrophages locally and distribute by different tissue sites. When uninfected sand fly feeds blood from an infected host, then it becomes infected with Amastigote. Next it transforms back into the Promastigote stage in the sand fly gut depending upon leishmania species and also individual host immune factors [7].

One of the pioneer scientists Marcos [8] applied differential equations for describing the TH1/TH2 model in order to adapt leishmanial disease with respect to immune response of cutaneous leishmaniasis. Das et al. [9] studied the dynamics of American Cutaneous Leishmaniasis with delay effect. Roy et al. [10] analyzed the transmission dynamics of cutaneous leishmaniasis to study the effects of delay based on disease transmission through the vector sand fly. Biswas et al. [11] introduced the concept of awareness programs driven by social media for controlling the disease cutaneous leishmaniasis. For reducing the transmission of leishmaniasis (in Morocco)

and controlling the vectors, Mejhed et al. [12] proposed the mathematical model with the effect of global climatic change. Langer et al. [13] recognized the biological issues that should be changed to minimize the parasite population in the host. First line of drugs as Sodium Stibogluconate (Pentostam) and Meglumine Antimoniate (Glucantime) are applied for treatment for this disease [14]. Oral and topical treatments are also available. But the drug induced control and impulsive therapies in the macrophage cell are yet to be explored.

In this research work, we have slightly changed the mathematical model of Nelson [15]. Modified model includes the early stage infection of macrophage cell (Promastigote) and late stage infection of macrophage cell (Amastigote) with two drug induced control therapies. The major target is to prevent the disease by controlling the parasite population in the macrophage cell over drugs. Initially, we have applied the drugs through impulsive strategy in fixed time interval to observe perfect adherence behavior of drugs. The model has been analyzed to find out the threshold time interval and minimum effectiveness of drugs. We have also observed that the effect of impulsive strategy in the non-fixed time interval on the system provides better expected result.

2. Mathematical Model with Basic Assumptions

Cytological behavior of macrophage has a great importance to study the disease cutaneous leishmaniasis. Macrophage cells are classified as susceptible macrophage cell and infected macrophage cell, where as the infected macrophage cell has two groups i.e., primary stage infected macrophage cell and late stage infected macrophage cell. We have formulated here a mathematical model with four components. They are susceptible macrophage cell (M_S), early stage infected macrophage cell, noted as Promastigote (M_P), late stage infected macrophage cell, named as Amastigote (M_A) and parasite population (P). We have considered λ as a constant source rate of macrophage and δ as the rate constant of change in macrophage status for individual immunity factor. The rate constant of infectivity is denoted by σ. State change factor from Promastigote to Amastigote stage is referred as K_m and burst size of Amastigote is noted as N_m. Finally α is the rate of loss of parasite population.

Here our motivation is to reduce the rate of infectivity that involves the interaction between susceptible macrophage and parasite. To do this task, we have introduced impulsive drug dose strategy to control the parasite population. However, continuous application of drug dose is neither possible nor desirable, so we shall assume drug dose occurs at distinct (not necessarily fixed) times t_k. At these times, the number of parasite in the macrophage are reduced by some proportion r. Thus incorporating the above assumption into our previous work [16], the mathematical model becomes:

$$\begin{aligned}
\tfrac{dM_S}{dt} &= \lambda + \delta M_P - \sigma M_S P - d_1 M_S, && t \neq t_k \\
\tfrac{dM_P}{dt} &= \sigma M_S P - \delta M_P - d_2 M_P - K_m M_P, && t \neq t_k \\
\tfrac{dM_A}{dt} &= K_m M_P - d_3 M_A, && t \neq t_k \\
\tfrac{dP}{dt} &= N_m d_3 M_A - d_4 P - \alpha P M_A, && t \neq t_k \\
\Delta P &= -rP, && t = t_k,
\end{aligned} \tag{2.1}$$

with the initial conditions $M_S(0) > 0$, $M_P(0) > 0$ $M_A(0) > 0$ and $P(0) > 0$. Moreover d_1, d_2, d_3 and d_4 are the death rates of susceptible macrophage, macrophage in Promastigote form, macrophage in Amastigote form and parasite population respectively. We have established the system is bounded for the condition given below:

$$K_m \sigma \lambda N_m > d_1 d_4 (\delta + d_2) + K_m d_1 d_4.$$

3. The System without Impulse

In this case, the model takes the following form:

$$\begin{aligned}
\tfrac{dM_S}{dt} &= \lambda + \delta M_P - \sigma M_S P - d_1 M_S, \\
\tfrac{dM_P}{dt} &= \sigma M_S P - \delta M_P - d_2 M_P - K_m M_P, \\
\tfrac{dM_A}{dt} &= K_m M_P - d_3 M_A, \\
\tfrac{dP}{dt} &= N_m d_3 M_A - d_4 P - \alpha P M_A,
\end{aligned} \tag{3.1}$$

with the initial conditions $M_S(0) > 0$, $M_P(0) > 0$, $M_A(0) > 0$ and $P(0) > 0$.

3.1. Existence Condition of Equilibria

The system (3.1) has two equilibrium points, given below as:

(i) Disease-free equilibrium $E_0(\widetilde{M_S},\widetilde{M_P},\widetilde{M_A},\widetilde{P})$ and another is

(ii) Endemic equilibrium $E^\star(M_S^\star,M_P^\star,M_A^\star,P^\star)$,

where $\widetilde{M_S}=\frac{\lambda}{d_1}$, $M_S^\star=\frac{\lambda-M_P^\star(K_m+d_2)}{d_1}$, $M_P^\star=\frac{d_3d_4P^\star}{K_m(N_md_3-\alpha P^\star)}$, $M_A^\star=\frac{d_4P^\star}{(N_md_3-\alpha P^\star)}$ and $P^\star=\frac{\sigma\lambda K_mN_md_3-d_1d_3d_4d_2-d_1d_3d_4\delta-d_1d_3d_4K_m}{\sigma\lambda\alpha K_m+\sigma d_3d_4K_m+\ \sigma d_3d_4d_2}$ with the condition $N_md_3>\alpha P^\star$.

The endemic equilibrium $E^\star$ is feasible if and only if $\frac{d_1d_4(\delta+d_2)}{K_m(\sigma\lambda N_m-d_1d_4)}>1$.

Remark 1: If the transmission factor of the disease (K_m) lies under its threshold value, then the system remains in disease-free situation. If we are able to control the parameter σ that is directly related to the explosion of the disease, then system can achieve the disease-free state. Similarly as N_m is directly related to the growth of parasite population, thus its lower value would enable to make the system free from disease.

3.1.1. Stability Analysis of the System

For finding basic reproduction ratio, three compartments $M_P{}'$, $M_A{}'$ and P' have been considered here. we have

$$\begin{bmatrix} M_P{}' \\ M_A{}' \\ P' \end{bmatrix} = \begin{bmatrix} -d_2-\delta-K_m & 0 & \sigma M_S \\ K_m & -d_3 & 0 \\ 0 & N_md_3-\alpha P & -d_4 \end{bmatrix} \begin{bmatrix} M_P \\ M_A \\ P \end{bmatrix}.$$

According to [17] the square matrix above can be re-written as the subtraction of two matrices. Thus, above matrix can be expressed as $Z'=(F-V)Z$. Here F is a non-negative matrix that contains the elements related to the generation of new infections and V is a diagonal non-negative matrix, which consists the elements related to the loss of infections. Considering that F corresponds to the infectivity function of an infected macrophage and V^{-1} is a diagonal matrix indicate loss of infected macrophage. Now at the trivial equilibrium point, ($\widetilde{M_S}=\frac{\lambda}{d_1},\widetilde{M_P}=\widetilde{M_A}=\widetilde{P}=0$), the matrix Next Generation Operator is, NGO$=FV^{-1}$,

where

$$F=\begin{pmatrix} 0 & K_m & 0 \\ 0 & 0 & N_md_3 \\ \frac{\sigma\lambda}{d_1} & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} d_2+\delta+K_m & 0 & 0 \\ 0 & d_3 & 0 \\ 0 & 0 & d_4 \end{pmatrix}.$$

This leads to

$$FV^{-1} = \begin{pmatrix} 0 & \frac{K_m}{d_3} & 0 \\ 0 & 0 & \frac{N_m d_3}{d_4} \\ \frac{\sigma\lambda}{(d_2+\delta+K_m)d_1} & 0 & 0 \end{pmatrix}.$$

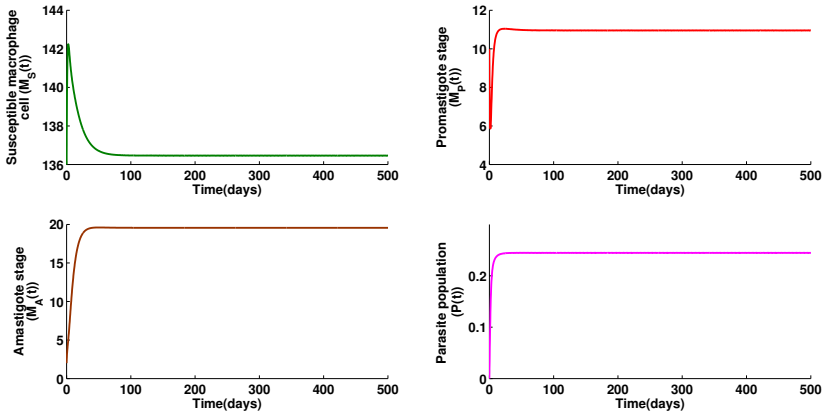

FIGURE 1. Population densities of the model variables for $R_0 > 1$ and other parameters are as in Table.

From above matrix, we can calculate the basic reproduction ratio from $det(NGO - \xi I) = 0$. The basic reproduction ratio is the dominant eigenvalue of the matrix. It follows the corresponding basic reproduction number $(R_0) = \frac{\sigma\lambda K_m N_m}{(\delta+d_2+K_m)d_1 d_4}$. If $R_0 < 1$, then the infection-free equilibrium is stable, while if $R_0 > 1$, then the infection-free equilibrium is unstable and infected equilibrium state exists.

Now the characteristic equation for the infected equilibrium state E^* is given below:

$$\kappa^4 + c_1\kappa^3 + c_2\kappa^2 + c_3\kappa + c_4 = 0,$$

where

$$
\begin{aligned}
c_1 &= \sigma P^\star + \alpha M_A^\star + d_1 + \delta + d_2 + K_m + d_3 + d_4 > 0,\\
c_2 &= d_4(\sigma P^\star + d_1 + \delta + d_2 + K_m + d_3) + d_3(\delta + d_2 + K_m + \alpha M_A^\star + \sigma P^\star + d_1)\\
&\quad + d_2(d_1 + \alpha M_A^\star + \sigma P^\star) + (\alpha M_A^\star + K_m)(d_1 + \sigma P^\star) + \delta(d_1 + \alpha M_A^\star) + \alpha M_A^\star K_m > 0,\\
c_3 &= d_3 d_4(\sigma P^\star + d_1 + \delta + d_2 + K_m) + d_3 d_1(d_2 + \alpha M_A^\star + K_m + \delta)\\
&\quad + d_3\alpha M_A^\star(\sigma P^\star + \delta + d_2 + K_m) + (\sigma P^\star K_m + \sigma P^\star d_2)(d_4 + \alpha M_A^\star + d_3)\\
&\quad + (d_1 d_2 + d_1 K_m)(d_4 + \alpha M_A^\star) + \delta d_1(\alpha M_A^\star + d_4) - \sigma M_S^\star K_m(N_m d_3 - \alpha P^\star) > 0\ ,\\
c_4 &= d_1 d_3(d_2 d_4 + d_2\alpha M_A^\star + K_m d_4 + K_m\alpha M_A^\star + \delta d_4 + \delta\alpha M_A^\star)\\
&\quad + (d_3 d_4\sigma P^\star + d_3\alpha M_A^\star\sigma P^\star)(d_2 + K_m) - d_1\sigma M_S^\star K_m(N_m d_3 - \alpha P^\star) > 0.
\end{aligned}
$$

From Routh-Hurwitz criterion, the necessary and sufficient condition for local asymptotical stability of the state are $c_1c_2 - c_3 > 0$ and $c_1(c_2c_3 - c_1c_4) - c_3^2 > 0$ are satisfied.

4. System with Impulsive Drug Dose

In this section, we have tried to see the effect of impulse with fixed drug dose to control the parasite in the macrophage cell. We have assumed the distinct time interval for applying the drug. As we are unable to distinguish the susceptible and infected parasite population in the macrophage cell, so when we apply the drug in the host cell, it affects both susceptible and infected macrophage cell population conjugately. During the drug management, the number of parasites (both susceptible and infected) in the macrophage cell are made less by some proportion r. The drug has not any fatal impact on human host population. Now the impulsive differential equation takes the form :

$$
\begin{aligned}
\frac{dP}{dt} &= \frac{N_m K_m \lambda}{d_2} - \left(\frac{K_m\alpha\lambda}{d_2 d_3} + d_4\right)P(t), \quad t \neq t_k,\\
\Delta P &= -rP, \qquad\qquad\qquad\qquad\quad t = t_k.
\end{aligned}
\tag{4.1}
$$

Here for single impulsive cycle $t_k \leq t \leq t_{k+1}$, the general solution is given by,

$$\begin{aligned} P(t) &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4} + e^{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_k - t)} P(t_k^+) - \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4} e^{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_k - t)}, \\ P_{k+1}^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\{1 - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_{k+1} - t_k)}\} + P_k^+ e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_{k+1} - t_k)}, \end{aligned} \tag{4.2}$$

where $P(t_k^+) = P_k^+, P(t_k^-) = P_k^-$. Now,

$$\begin{aligned} P_1^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}, P_1^+ = (1-r)\frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}, \\ P_2^- &= (1-r)\frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4} e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_2 - t_1)} + \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\{1 - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_2 - t_1)}\}, \\ P_2^+ &= (1-r)P_2^- = (1-r)^2 \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4} e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_2 - t_1)} \\ &\quad + (1-r)\frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\{1 - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_2 - t_1)}\}, \\ P_3^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}[(1-r)^2 e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_3 - t_1)} + (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_3 - t_2)} \\ &\quad + 1 - (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_3 - t_1)} - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_3 - t_2)}], \\ P_4^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}[(1-r)^3 e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_4 - t_1)} + (1-r)^2 e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_4 - t_2)} \\ &\quad + (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_4 - t_3)} + 1 - (1-r)^2 e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_4 - t_1)} \\ &\quad - (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_4 - t_2)} - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_4 - t_3)}]. \end{aligned}$$

Therefore the general solution becomes,

$$\begin{aligned} P_n^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}[(1-r)^{(n-1)} e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n - t_1)} + (1-r)^{(n-2)} e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n - t_2)} \\ &\quad + ... + (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n - t_{n-1})} + 1 - (1-r)^{(n-2)} e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n - t_1)} \\ &\quad - (1-r)^{(n-3)} e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n - t_2)} - ... - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n - t_{n-1})}]. \end{aligned} \tag{4.3}$$

This is the general solution for the maximal number of parasite present in the macrophage cell before drug dosing application. For fixed time interval the solution does not depend on time.

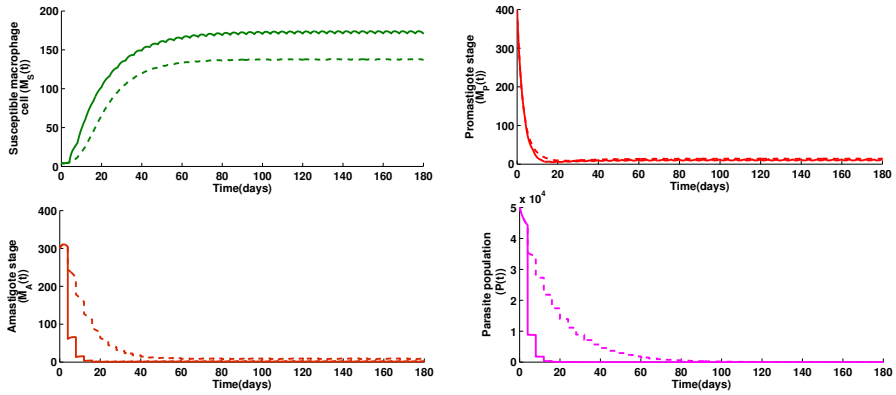

FIGURE 2. The system behavior for $r = 20\%$ (denoted by - - -) and for $r = 80\%$ (denoted by —).

4.1. Drug Dose for Fixed Time Interval

For fixed time period, i.e., $\tau = t_{n+1} - t_n$ is constant, then we have,

$$\begin{aligned} P_n^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\Big[1 + (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau} + (1-r)^2 e^{-2\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau} \\ &\quad + \ldots + (1-r)^{(n-1)} e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)(n-1)\tau} - e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}\Big\{1 + (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau} \\ &\quad + \ldots + (1-r)^{(n-2)} e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)(n-2)\tau}\Big\}\Big] \\ &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\left[\frac{1-(1-r)^n e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)n\tau}}{1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}}\right. \\ &\quad \left. - e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}\frac{1-(1-r)^{(n-1)} e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)(n-1)\tau}}{1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}}\right]. \end{aligned} \tag{4.1.1}$$

Therefore,

$$\begin{aligned} \lim_{n\to\infty} P_n^- &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\left[\frac{1}{1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}}\right. \\ &\quad \left. - e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}\frac{1}{1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}}\right] \\ &= \frac{N_m K_m \lambda d_3}{K_m \alpha\lambda + d_2 d_3 d_4}\left[\frac{1-e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}}{1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2d_3}+d_4\right)\tau}}\right]. \end{aligned} \tag{4.1.2}$$

This gives the maximum value of the infected macrophage cell. To keep this under the threshold value $\tilde{P}$ we have,

$$\frac{N_m K_m \lambda d_3}{K_m \alpha \lambda + d_2 d_3 d_4}\Big[\frac{1-e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)\tau}}{1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)\tau}}\Big] < \tilde{P},$$

which implies $\tau < \frac{1}{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)} \ln\{\frac{\frac{N_m K_m\lambda d_3}{K_m\alpha\lambda+d_2d_3d_4}-\tilde{P}(1-r)}{\frac{N_m K_m\lambda d_3}{K_m\alpha\lambda+d_2d_3d_4}-\tilde{P}}\} = \tau_{max}(r)$ (say).

Remark 2: If the time interval τ be always less than some predetermined quantity i.e., τ_{max}, then we are able to control the parasite population in the macrophage cell under the threshold value $\tilde{P}$.

4.2. Drug Dose for Non-Fixed Time Interval

Limited resources and inadequate infrastructure is the major challenge in the process of the regular disease control. Thus applying drug at fixed intervals may be a difficult task. Thus for non fixed drug dose, we try to find out the most possible "next best" drug applying time interval to keep under control the parasite population below $\tilde{P}$. We assume that two most recent drug dose event is known.

Then, $e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_k)} \approx 0$, for $k > 2$.

Thus we have,

$$\begin{aligned} P_n^- \approx\ & \frac{N_m K_m \lambda d_3}{K_m\alpha\lambda + d_2 d_3 d_4}\Big[(1-r)^2 e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_{n-2})} + (1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_{n-1})} \\ & +1-(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_{n-2})} - e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_{n-1})}\Big] < \tilde{P}, \end{aligned}$$

$$\Rightarrow 1-r(1-r)e^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_{n-2})} - re^{-\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)(t_n-t_{n-1})} < \frac{K_m\alpha\lambda+d_2d_3d_4}{N_m K_m\lambda d_3}\tilde{P},$$

Hence, the "next best" drug dosing time satisfies,

$$t_n < \frac{1}{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)} \ln\Big[\frac{r(1-r)e^{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)t_{n-2}} + re^{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)t_{n-1}}}{1-\frac{K_m\alpha\lambda+d_2d_3d_4}{N_m K_m\lambda d_3}\tilde{P}}\Big].$$

For $r = 1$, we have $t_n - t_{n-1} = \widetilde{\tau}$, (say)

$$\Rightarrow \widetilde{\tau} < \frac{1}{\left(\frac{K_m\alpha\lambda}{d_2 d_3}+d_4\right)} \ln\Big[\frac{N_m K_m\lambda d_3}{N_m K_m\lambda d_3-(K_m\alpha\lambda+d_2d_3d_4)}\Big] \approx \tau_{max}(1).$$

Thus to compare for fixed and non-fixed drug dose when $r = 1$, the two options are equivalent.

If $r = 0$ for non-fixed drug dosing interval,

$$P_n^- \approx \frac{N_m K_m \lambda d_3}{K_m \alpha \lambda + d_2 d_3 d_4} \left[e^{-2\left(\frac{K_m \alpha \lambda}{d_2 d_3} + d_4\right)\widetilde{\tau}} + e^{-\left(\frac{K_m \alpha \lambda}{d_2 d_3} + d_4\right)\widetilde{\tau}} + 1 - e^{-2\left(\frac{K_m \alpha \lambda}{d_2 d_3} + d_4\right)\widetilde{\tau}} - e^{-\left(\frac{K_m \alpha \lambda}{d_2 d_3} + d_4\right)\widetilde{\tau}} \right]$$

$$= \frac{N_m K_m \lambda d_3}{K_m \alpha \lambda + d_2 d_3 d_4}.$$

For $\tilde{P} < P_n^-$, and if $\widetilde{\tau}_{max} = 0$, then

$$r = 1 - \frac{K_m \alpha \lambda + d_2 d_3 d_4}{N_m K_m \lambda d_3} \tilde{P},$$

$$r = 1 + \frac{K_m \alpha \lambda + d_2 d_3 d_4}{N_m K_m \lambda d_3} \tilde{P}.$$

It follows that first root is greater than zero and second root is larger than one. Hence the minimum degree of effectiveness is required for non-fixed drug dose only when $r_1 < r \leq 1$, where

$$r_1 \equiv 1 - \frac{K_m \alpha \lambda + d_2 d_3 d_4}{N_m K_m \lambda d_3} \tilde{P}.$$

Remark 3: Thus, by assuming two previous drug dosing times are known for non-fixed time interval, we can conclude the "next best" drug applying time. For non-fixed case, there is an additional requirement of minimum efficacy, but both can control the disease.

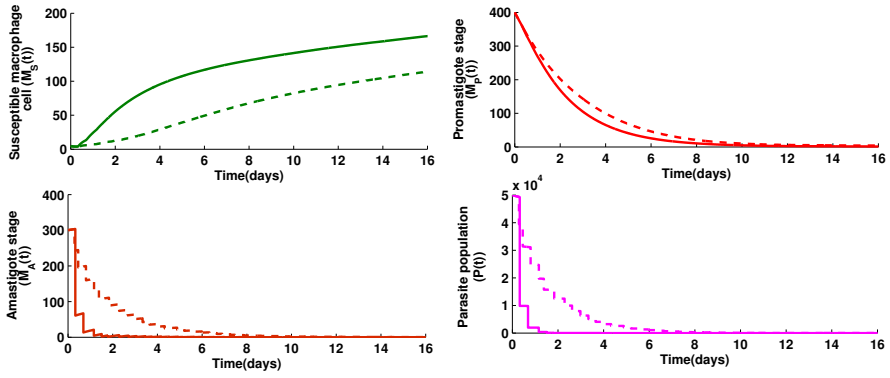

FIGURE 3. The system behavior for non-fixed interval for $r = 20\%$ (denoted by - - -) and for $r = 80\%$ (denoted by —).

5. Sensitivity Analysis

Definition: The normalized forward sensitivity index [20] of a variable say x, that depends continuously on a parameter say y, is denoted by,

$$\Upsilon_y^x = \frac{\partial x}{\partial y} \times \frac{y}{x}.$$

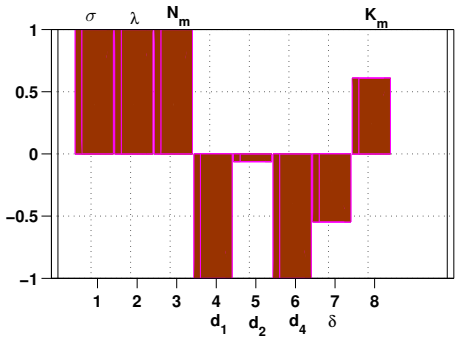

FIGURE 4. Tornado plot of sensitivity analysis of all eight parameters that influence R_0.

The sensitivity analysis is introduced to study the strength of the basic reproductive ratio R_0 for the model parameters. This analysis assists us to classify the parameters, which preserves the high influence on the diseases transmission, i.e., to the reproductive number. We have here developed a sensitivity index by applying the partial derivatives, whenever the variable is a differentiable function of the model parameter.

$$\sigma_{Sen} = \frac{\partial R_0}{\partial \sigma} \times \frac{\sigma}{R_0} = \frac{\lambda K_m N_m}{(\delta + d_2 + K_m) d_1 d_4} \times \frac{\sigma}{R_0}.$$

In the same way we can find sensitivity indices with respect to the other model parameters.

6. Numerical Simulation

Table. *List of parameters used in the model (2.1)*

Parameter	Range	Default Value	Reference
λ	$10 - 20\text{mm}^3\text{day}^{-1}$	10	[15]
δ	$0.25 - 0.36\text{day}^{-1}$	0.35	[15]
σ	$0.18 - 0.29\ \text{day}^{-1}$	0.21	*Assumed*
K_m	$0.25 - 0.43\ \text{day}^{-1}$	0.28	[15]
N_m	$0.18 - 0.36\text{mm}^3\text{day}^{-1}$	0.28	*Assumed*
α	$0.15 - 0.23\ \text{day}^{-1}$	0.15	[15]
d_1	$0.04 - 0.08\ \text{day}^{-1}$	0.05	[15]
d_2	$0.03 - 0.052\ \text{day}^{-1}$	0.04	[15, 21]
d_3	$0.02 - 0.24\ \text{day}^{-1}$	0.14	[15, 21]
d_4	$0.12 - 0.25\ \text{day}^{-1}$	0.2	[15]

In this section, we have studied the mathematical model with impulsive behaviour in (4.1) through numerical simulation. The values of parameters for numerical simulations are given in the Table. From the existence and stability analysis for the system, K_m, σ and N_m seem to be important parameters. System dynamics of the model without drug is shown in Figure 1. Here, it is observed that when state change factor $K_m > 0.28$ with $\sigma = 0.21$ and $N_m = 0.24$, the system goes to infected state condition. But if $K_m < 0.28$, the system moves to infection-free state and the disease does not persist.

The impacts of drug dose are exhibited in Figure 2. Here we have considered $r = 0.2$ and $r = 0.8$ with time interval $\tau = 4$. It is clearly observed that in presence of drug dose with perfect adherence (keeping four days interval), the infected system moves to infection-free state. Also if we increase the power of drug dose, the system moves towards better outcome. If the effectiveness of drug dose is 20%, the system achieves better result after 30 days or more than that. But if we increase the effectiveness to 80%, the system gives more better output (i.e., uninfected cell population increases more quickly). Thus effectiveness of the drug dose gives a superior impact on the model to move the system towards its disease-free situation. Evidently

form Figure 2, it is clear that infected macrophage cell goes to zero level by proper choosing frequency and strength.

The effects of non-fixed drug dose are represented in Figure 3. Here we have considered $r = 0.2$ and $r = 0.8$. It is clearly observed that in presence of drug dose with perfect adherence, the infected system moves to infection-free state. Moreover, if the power of drug dose is increased, the system moves towards more healthy situation. If the effectiveness of drug dose is 20%, the system achieves better position after 4 days or more than that. But if we increase the effectiveness to 80%, much more enhanced situation is attained. In other words, uninfected cell population is increased more rapidly. Thus effectiveness of the drug dose provides a superior effect on our proposed system moving towards the healthy situation.

Figure 3 illustrates for non fixed drug dose, where we try to find out the most possible "next best" drug dosing time interval to control the parasite population below $\tilde{P}$. Keeping the drug dose interval effectiveness from 20% to 80%, it is observed that suitable "next best" drug dosing interval can support us giving much better outcomes compared to the fixed spraying.

Tornado plot of the normalized sensitivity index for different parameters is represented in Figure 4. If the sensitivity index is positive, then R_0 increases along with increasing value of parameter. But if sensitivity index is negative, then with decreasing value of parameter, R_0 is decreased. State change factor K_m (from Promastigote to Amastigote stage), σ and N_m are the crucial parameters that have significant effects on the system. So from the Figure 4, it is concluded that the basic reproduction ratio depends on the state change factor of macrophage cell (K_m) more scientifically. Simultaneously, the parameters σ and N_m are more sensitive rather the other parameters. The parameter λ i.e., the constant rate of source of macrophage cell (uninfected) is positively sensitive but we do not take into account the parameter because our study is mainly based on infected macrophage cells. Moreover death rates of susceptible macrophage cell (d_1) and parasite population (d_4) are negatively sensitive. The change of the behavioral pattern of the system dynamics depends on rate constant of infectivity, state change factor and burst size of infected macrophage cell more effectively. So if we can reduce the infectivity rate of macrophage cell, the disease can automatically be kept under control.

7. Discussion

Control of the parasite population is one of the efficient approaches to exterminate the disease cutaneous leishmaniasis. In this connection, dosing of drug performs a responsible function for controlling the disease. For $R_0 > 1$, the infection-free state drops its stability and the system tends towards the infected condition. Susceptible macrophage cell is sharply decreased up to 17 days (approx.) and early stage infected macrophage cell population is gradually increased up to more or less 35 days (approx.), when the disease exists. The threshold values of time interval with minimum degree of effectiveness is obligatory for drug dose for fixed time interval. For non-fixed case, there is an additional requirement of minimum efficacy, but both can control the disease. So the disease can be restricted by suitable drug dose with moderate frequency and strength. Also, infectivity rate, burst size and the state change factor from Promastigote stage to Amastigote stage of infected macrophage cell is considered to be more sensitive.

8. Conclusion

The disease transmission can be terminated with regulated drug dosing of judicious strength and moderate frequency. For drug dose applying in a four days interval, the infected cells move to uninfected state. The system reaches towards healthy state, if the drug dose concentration is enhanced. Hence the effectiveness of the drug dose motivates the system moving towards the infection-free healthy state. Drug administration through impulsive mode is much better as the dose is not one time application. It can be used repeatedly for better outcome to control the disease. Although complete eradication of cutaneous leishmaniasis is too much tough and difficult in realistic scenario but if our research findings can be applied to infected topographical region, then we can enlighten a new horizon to combat against cutaneous leishmaniasis in global perceptive.

Conflict of Interests

The authors declare that there is no conflict of interests.

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