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Sensitivity and Optimal Control Analysis of Japanese Encephalitis Disease: A Mathematical Model

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Abstract: Japanese encephalitis is caused by flavivirus, which can affect both humans and animals. A Japanese encephalitis disease model is proposed and analyzed to investigate the transmission dynamics of Japanese encephalitis with saturated incident rate and saturated treatment function. Assume that the infected pig populations are growing logistically in the environment. The basic reproduction number $(\mathcal{R}_0)$ of the model is obtained using the next-generation matrix method. The sensitivity analysis is performed to identify the key parameters that affect the basic reproduction number, which can be regulated to control the transmission dynamics of the disease. The model is extended to optimal control model incorporating three time-dependent inputs for the control of transmission route by using Pontryagin's maximum principle. This study is significant as Japanese encephalitis disease poses serious challenges for public health in past few years. Numerical simulation is performed to support our analytical findings.

Keywords: japanese encephalitis, basic reproduction number, sensitivity, optimal control, simulation

1. INTRODUCTION

The Japanese encephalitis is primarily a mosquito-borne rural disease, which is transmitted to human through the bite of an infected Culex species mosquitoes. Japanese encephalitis virus (JEV) is a flavivitus of the family of flaviviridae like the viruses of the Yellow fever, West Nile, and Dengue. The virus is transmitted in an enzootic cycle among mosquitoes and vertebrate amplifying hosts, primarily domestic pigs and/or water birds (Wild Heron) [1, 2]. Most impotently there is no such type of evidence for human to human transmission. The first case of JEV disease was recorded in 1871 in Japan [3]. The clinical cases of Japanese encephalitis globally estimated every year nearly 68,000, with approximately 13,600 to 20,400 deaths. The Japanese encephalitis primarily affects children less than 15 years of age. The fatality rate varies between $20\% - 40\%$, but it may reach 58% and over. The incubation period for Japanese encephalitis is between 4–14 days [1, 3]. The primary symptoms of the disease includes fever, chills, headache, and vomiting. Other symptoms like neurological symptoms, drowsiness, dizziness, confusion, abdominal pain and diarrhea might develop over the next few days [5]. There is no specific medicine for treatment, but patients should be hospitalized for supporting care. During the infected period of Japanese encephalitis, people should drink plenty of fluids and rest sufficiently. The vaccine is available to control Japanese encephalitis virus disease but it does not protect 100 $\%$. Japanese encephalitis virus has been identified most common in rural areas in southeast Asia, Eastern Asia, Southeastern Asia, and Pascific Island. The disease is investigated globally in the following territories : Australia, Bangladesh, Bruni, Burma, Cambodia, China, Guam, India, Indonesia,

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Japan, Laos, Malaysia, Nepal, North Korea, Pakistan, Phillipines, Russia, Saipan, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, Timor-Leste, Vietnam. The main vector of Japanese encephalitis is C. Annulirostris. In Indian condition many other secondary vectors have reported including Anopheles subpictus, A. peditaeniatys, C.epidesmus, C.gelidus, C.whitmorei, C. pseudovishnui, M. uniform and Mansonia indiana. Pigs are considered to be principal amplifying host in India. The transmission is possible between May and September. The first case of Japanese encephalitis disease was diagnosed in 1955 in Tamil Nadu in India [4]. Consequently, several major out-breaks have been listed from different parts of the country, mostly in rural areas of Assam, Bihir, Harayana,Karnataka, Tamil Nadu, Uttar Pradesh. In India, 1,500 to 4000 JEV cases are reported every year [3]. According to National health mission in Assam most of the upper Assam districts, including Dibrugarh, Golaghat, Jorhat, Lakhimpur and lower Assam district of Kamrup have been badly affected every year by the Japanese encephalitis mosquito-borne disease.

Several mathematical models have been studied and analyzed the dynamics of Japanese encephalitis transmission [3-13] as yet. In [3], authors discussed the current knowledge of the epidemiology and the parthenogenesis of this deadly disease have been summarized. In [4], authors deals with application of various control strategies to Japanese encephalitis among human, pig and mosquito. In [5], authors proposed a mathematical model for the spread of Japanese encephalitis with emphasis on the environmental effects on the aquatic phase of mosquitoes. In [6], authors proposed a mathematical model with impact of vaccination on of JE with standard incidence rate of mosquitoes, pigs and humans. In [7], authors has been studied stability and bifurcation analysis of Japanese encephalitis model with/without effect of some control parameters. In [8] authors developed a mathematical model and analysis the spread of Japanese encephalitis with environmental effects. In [9] authors build an SIRS epidemic model of Japanese encephalitis and discussed analytically. In [10], authors have formulated a deterministic model with saturated treatment function and found that north east states of India need better treatment and awareness about the disease. In [11], author contracted a mathematical model with saturated incidence function and analysis optimal control theory. In [12], author discussed different causes of backward bifurcations in some epidemiological models. In [13] authors formulated a mathematical model and regulate important parameters in the spread of the disease through the sensitivity analysis.

In this paper, we have constructed a Japanese encephalitis mathematical model by considering standard incidence type interaction with saturated incident and saturated treatment. As India is a developing countries, so treatment may not available for all if the number of infectives are very large. So in the present study we have incorporated the saturated treatment as discussed in [10]. The remaining part of the paper is organized as follows: Section 2 describes the model and established biological feasible region; Section 3 presents basic reproduction number; Section 4 deals with data; Section 5 deals with sensitivity analysis of basic reproduction number $\mathcal{R}_0$; Section 6 describes optimal control problem; section 7 demonstrates the numerical simulation of optimal control and finally Section 8 concludes the paper.

2. THE MODEL FORMULATION

The model consists six different compartments such as Susceptible humans (S_h), Infected humans (I_h) and Recovered humans (R_h), Susceptible Japanese encephalitis mosquitoes (S_j), Infected Japanese encephalitis mosquitoes (I_j), and Infected pigs (I_p). Many epidemic models has been used bilinear incident rate to prevent and control the spread of the infectious disease. Here we introduced saturated incident rate in the proposed model as saturated incident rate is more suitable than bilinear incident rate. Based on following assumption the system of differential equations formulated.

- $\frac{\beta_1 S_h I_j}{1+kI_h}$ is the saturated incident rate, which tends to a saturated level when I_h gets large, $\beta_1 I_j$ measures the infection force when disease is entering a fully susceptible population [14].
- $\beta_1 S_h I_j$ is known as bilinear incidence rate and $\frac{1}{1+kI_h}$ measures the inhibition effect from the behavioral change of susceptible individuals when their number increases or from the crowding effect of the infective individuals [9, 14, 15].
- $\frac{1}{1+kI_h}$ is the incidence rate which is more reasonable than the $\beta_1 S_h I_j$ (bilinear incidence rate), [10].
- Assume that through treatment the infected individuals recover at a saturated function $h(I_h) = \frac{\gamma_h I_h}{1+\alpha I_h}$, where γ_h is recovery rate. When $\alpha = 0$, the saturated treatment function becomes linear [14, 16–18].
- The model is a non-linear standard incidence type interaction between human and mosquitoes.
- The individuates are recruited in the region at a constant rate Λ_h and they join the susceptible class.
- The susceptible individuals become infected when the mosquito bites and join the infected human class at the rate of β_1.
- Infected individuals get treatment and recover from encephalitis with recovery rate γ_h and join recover class.
- The susceptible Japanese encephalitis mosquitoes becomes infected and join infected mosquitoes class at the rate β_2.
- Susceptible mosquitoes bite the infected pigs and becomes infected at the rate β_3.
- The infected pig population are growing logistically.

Keeping in view the above facts, the mathematical model is framed as follows:

$$\begin{cases} \frac{dS_h}{dt} = \Lambda_h - \beta_1 S_h \left(\frac{I_j}{1+kI_h}\right) - \mu_h S_h + \delta_h R_h \\ \frac{dI_h}{dt} = \beta_1 S_h \left(\frac{I_j}{1+kI_h}\right) - \frac{\gamma_h I_h}{1+\alpha I_h} - (\mu_h + \mu_1) I_h \\ \frac{dR_h}{dt} = \frac{\gamma_h I_h}{1+\alpha I_h} - (\delta_h + \mu_h) R_h \\ \frac{dS_j}{dt} = \Lambda_j - \beta_2 S_j \frac{I_h}{N_h} - \beta_3 S_j I_p - \mu_j S_j \\ \frac{dI_j}{dt} = \beta_2 S_j \frac{I_h}{N_h} + \beta_3 S_j I_p - \mu_j I_j \\ \frac{dI_p}{dt} = r I_p \left(1 - \frac{I_p}{K}\right) - \mu_p I_p \end{cases} \tag{2.1}$$

2.1. Positivity and Boundedness

Here, we shall show that the positivity and boundedness of the population. From the system (1), we have

$$\left.\frac{dS_h}{dt}\right|_{S_h=0} = \Lambda_h + \delta_h R_h > 0, \quad \left.\frac{dI_h}{dt}\right|_{I_h=0} = \beta_1 S_h I_j \geq 0,$$

Table 2.1. Description of biological parameters

Parameter	Description	Value
Λ_h	Rate of recruitment of human population	20
Λ_j	Rate of recruitment of vector(mosquito)	40
β_1	Transmission probability interaction between S_h and I_j	0.00256
β_2	Transmission probability interaction between S_j and I_h	.031
β_3	Transmission probability interaction between S_j and I_p	0.013
α	A positive constant	0.02
γ_h	Recovery rate of human population	0.005
δ_h	Rate at which recovered human become susceptible due to loos of immunity	0.05
μ_h	Natural mortality rate of human population	0.0421
μ_1	Mortality rate of human due to infection	0.0326
μ_j	Natural mortality rate of vector	0.112
μ_p	Natural mortality rate of pigs	0.51
r	The growth rate coefficient of infected pigs	2
K	Carrying capacity of mosquito population	10

$$\frac{dR_h}{dt}\Big|_{R_h=0} = \frac{\gamma_h I_h}{1+\alpha I_h} \geq 0, \quad \frac{dS_j}{dt}\Big|_{S_j=0} = \Lambda_j > 0,$$

$$\frac{dI_j}{dt}\Big|_{I_j=0} = \beta_2 S_j \frac{I_h}{N_h} + \beta_3 S_j I_p \geq 0,$$

$$\frac{dI_p}{dt}\Big|_{I_p=0} \geq 0$$

Here, all the rates are non-negative, so if we start in the interior of the non-negative bounding R^6, we shall always remain in this cone keeping mind of the fact that direction of the vector field is inward on all the bounding planes. We note the change rate of the total population $N_h = S_h + I_h + R_h$ and $N_j = S_j + I_j$ are given by the following differential equations :

$$\begin{aligned} \frac{dN_h}{dt} &= \Lambda_h - \mu_h N_h - \mu_1 I_h, \\ \frac{dN_j}{dt} &= \Lambda_j - \mu_j N_j. \end{aligned}$$

This gives $\limsup_{t\to\infty} N_h \leq \frac{\Lambda_h}{\mu_h}, \limsup_{t\to\infty} N_j \leq \frac{\Lambda_j}{\mu_j}$. Therefore, all $S_h(t), I_h(t), R_h(t)$ are bounded by $\frac{\Lambda_h}{\mu_h}$ and the solutions $S_j(t), I_j(t)$ are bounded by $\frac{\Lambda_j}{\mu_j}$. Hence, the biological feasible region of the proposed system (1) is given by the following positively invariant region:

$$\Omega = (S_h, I_h, R_h, S_j, I_j, I_p) \in R_+^6 : (S_h + I_h + R_h) \leq \frac{\Lambda_h}{\mu_h}, (S_j + I_j) \leq \frac{\Lambda_j}{\mu_j}.$$

3. BASIC REPRODUCTION NUMBER

The disease-free equilibrium for the system (2) as follows E_0=$(N_h^0, I_h^0, R_h^0, N_j^0, I_j^0, I_p^0) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_j}{\mu_j}, 0, 0\right)$.

The reproduction number $\mathcal{R}_0$ gives the average number of infected individuals generated by the one in a fully susceptible population and for our model, it is given by the above expression of $\mathcal{R}_0$. Mathematically, $\mathcal{R}_0$ is a threshold parameter for the stability of a disease-free equilibrium and is related to the highest and final size of an epidemic. To find the basic reproduction number $\mathcal{R}_0$, we consider $\left(\frac{dI_h}{dt}, \frac{dR_h}{dt}, \frac{dI_j}{dt}, \frac{dI_p}{dt}\right)$ and using the next-generation matrix method as described in [19, 20]. The matrix $\mathcal{F}$ and $\mathcal{V}$ as follows:

$$\mathcal{F} = \begin{pmatrix} \beta_1(N_h - I_h - R_h)\dfrac{I_j}{1+kI_h} \\ 0 \\ \beta_2(N_j - I_j)\dfrac{I_h}{N_h} + \beta_3(N_j - I_j)I_p \\ 0 \end{pmatrix},$$

$$\mathcal{V} = \begin{pmatrix} \dfrac{\gamma_h I_h}{1+\alpha I_h} + (\mu_h + \mu_1)I_h \\ -\dfrac{\gamma_h I_h}{1+\alpha I_h} + (\delta_h + \mu_h)R_h \\ \mu_j I_j \\ -rI_p\left(1 - \dfrac{I_p}{K}\right) + \mu_p I_p \end{pmatrix}$$

Now the matrix F (Jacobian of $\mathcal{F}$ at disease-free equlibrium E_0) and V(Jacobian of $\mathcal{V}$ at disease-free equilibrium E_0) are obtain as

$$F = \begin{pmatrix} 0 & 0 & \beta_1 N_h^0 & 0 \\ 0 & 0 & 0 & 0 \\ \beta_2 \dfrac{N_j^0}{N_h^0} & 0 & 0 & \beta_3 N_j^0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \gamma_h + \mu_h + \mu_1 & 0 & 0 & 0 \\ -\gamma_h & \mu_h + \mu_p & 0 & 0 \\ 0 & 0 & \mu_j & 0 \\ 0 & 0 & 0 & -r + \mu_p \end{pmatrix}$$

The largest eigenvalue of FV^{-1} is called the basic reproduction number R_0 and is obtained as follows:

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \dfrac{\beta_1 N_h^0}{\mu_j} & 0 \\ 0 & 0 & 0 & 0 \\ \beta_2 \dfrac{N_j^0}{N_h^0(\gamma_h + \mu_h + \mu_1)} & 0 & 0 & \dfrac{\beta_3 N_j^0}{\mu_p - r} \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

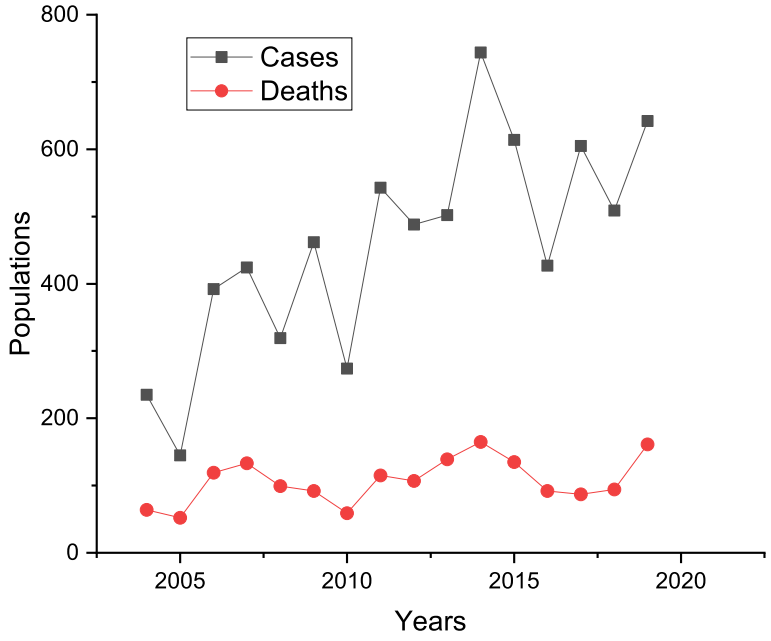


Fig. 4.1. Trend of Japanese Encephalitis cases in Assam, India during 2004-2019

The spectral radius of the matrix FV^{-1} is called the basic reproduction number $\mathcal{R}_0$ and is obtained as follows:

$$\mathcal{R}_0 = \sqrt{\frac{\beta_1\beta_2\Lambda_j}{\mu_j^2(\gamma_h+\mu_h+\mu_1)}}$$

The quantity $\mathcal{R}_0$ is knownas basic reproduction number, the expected number of secondary cases produced in completely susceptible population, by a typical infective individual,

4. DATA SCENARIO

In India, approximately 597,542,000 people are live in Japanese encephalitis region, and every year 1,500 to 4,000 japanese encephalitis cases are reported. Here, from 2004 to 2019 annual reported cases of japanese encephalitis are using for graphical representation. For this study, we consider two states of India which are Assam and Uttar Pradesh as these are Japanese Encephalitis infected states of India. The total reported cases from 2004 to 2019 in Assam and Uttar Pradesh are 7,325 and 33,572, which are demonstrated in Figure 1 and 2 respectively. In Uttar Pradesh highest number of cases were reported in 2006 and lowest number of cases were reported in 2019. In Assam highest number of cases were reported in 2014 and lowest number of cases were reported in 2005.

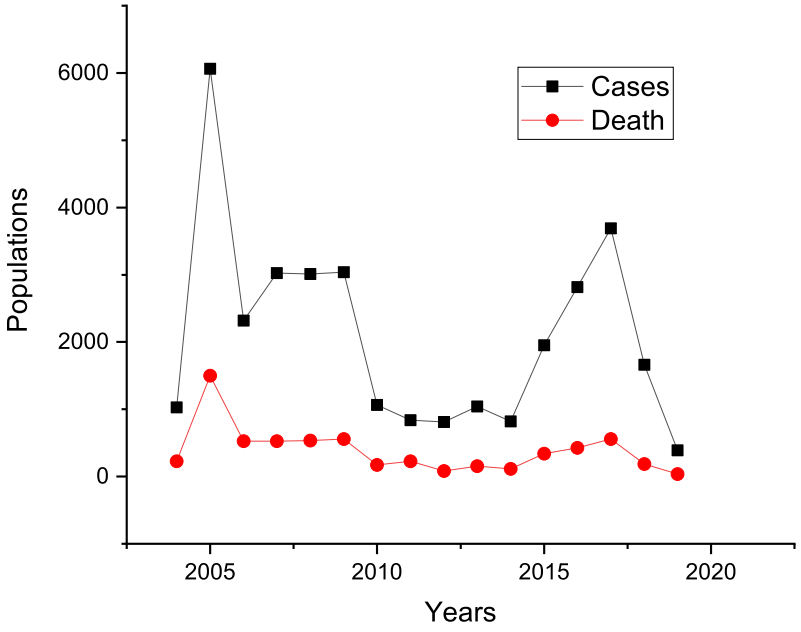


Fig. 4.2. Trend of Japanese Encephalitis cases in Uttar Pradesh, India during 2004-2019

5. SENSITIVITY ANALYSIS OF $\mathcal{R}_0$

To visualize the effect of the parameters involved in the expression of basic reproduction number $\mathcal{R}_0$, we calculated the normalized forward sensitivity indices of $\mathcal{R}_0$ to those parameters [21]. We keep the parameters at the same values as in Table 1. The normalized forward sensitivity index of a variable to a parameter is determined by the ratio of the relative change in the variable to the relative change in the parameter [13]. The sensitivity indices of $\mathcal{R}_0$ with respect to the parameters of interest are depicted in Figure 3, 4 and 5. The figure shows that when the parameters β_1, β_2, and Λ_j increase, keeping the other parameters constant, the value of $\mathcal{R}_0$ increases as these parameters have positive indices. Instead, increase in the values of parameters γ_h, μ_h, μ_1, and μ_j leads to decrease in the values of $\mathcal{R}_0$ as they have negative indices. It is noted that the sensitivity index of $\mathcal{R}_0$ is 0.5 for the parameters $\beta_1, \beta_2, \Lambda_j$. It means that 0.5% increase in the values of any of these parameters, keeping other parameters fixed, will result in 0.5% increment in the value of $\mathcal{R}_0$. Precisely, lower values of $\mathcal{R}_0$ are of crucial importance as they increase the chances of disease eradication. Therefore,it is imperative to prevent an increase in the parameters having positive sensitivity indices whereas increasing the values of parameters having negative indices is instead preferred.Thus, any prevention measure aiming at reducing the former parameters and increasing the latter must be taken into serious consideration. If such variable is differentiable with respect to the parameter, then the sensitivity index is defined using partial derivatives, [13]. The normalized forward sensitivity index of $\mathcal{R}_0$, which is differentiable with respect to a given parameter P, is defined by

$$Y_P^{\mathcal{R}_0} = \frac{P}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial P}$$

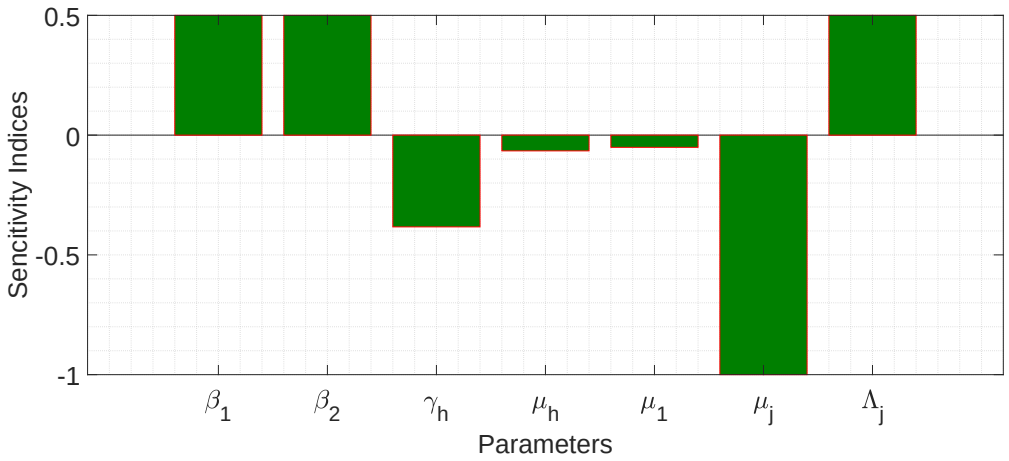


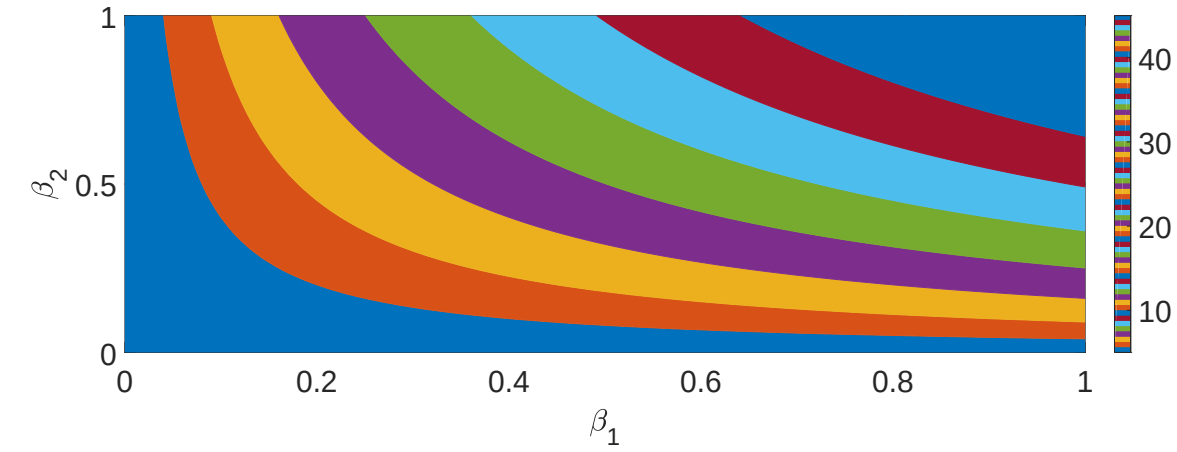
Fig. 5.3. Normalized forward sensitivity indices of $\mathcal{R}_0$ with respect to model parameters. Parameter values : $\beta_1 = 0.00256, \beta_2 = 0.031, \gamma_h = 0.245, \mu_h = 0.0421, \mu_1 = 0.0326, \mu_j = 0.112, \Lambda_j = 40$

The above formula can be used to compute the analytical expression for the sensitivity of $\mathcal{R}_0$ to each parameter that it includes. Plotted contour plot of some key parameters on $\mathcal{R}_0$. If we increase or decrease the value of β_1 and β_2, and then the value of $\mathcal{R}_0$ will increase or decrease, respectively, which is shown in Figure 4(a). Also, we can conclude that increasing the value of Λ_j will increase the value of the $\mathcal{R}_0$, but if we increase the value of μ_j, it will decrease the value of the $\mathcal{R}_0$, which is the death rate of the mosquito, and this is the one of the best control policy to reduce the disease infection from the population, manifest in Figure 4(b). Similarly other significant changes of $\mathcal{R}_0$ are shown in Figures 4(c) and 5(a,b,c) based respective parameters. So, the correct estimation of these parameters is very important to predict transmission of this disease.

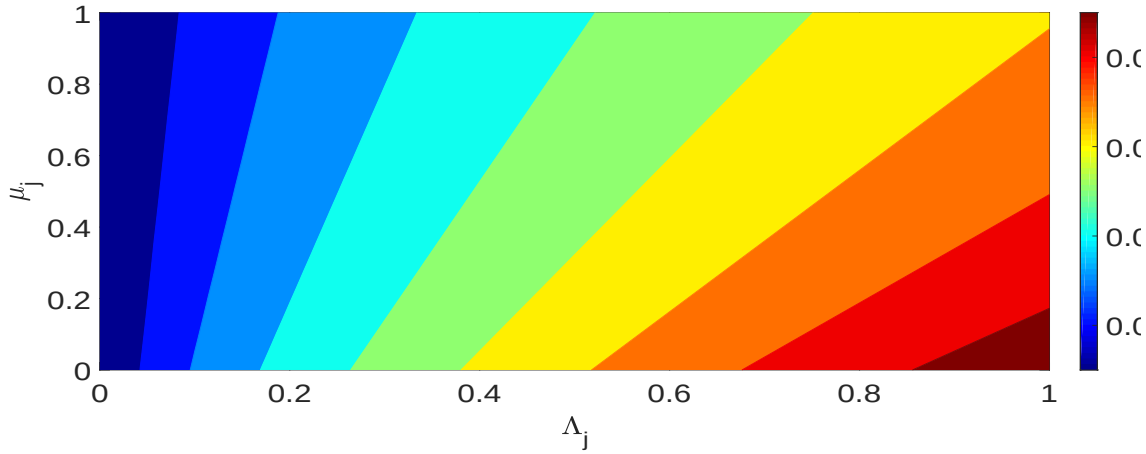
6. OPTIMAL CONTROL PROBLEM

In this section, three different types of control intervention viz., $u_1(t), u_2(t), u_3(t)$ are incorporated into the model system (1) and extended to optimal control problem. There interventions are implementing either pharmaceutical(treatment) or non-pharmaceutical(effect of information). The main goal this research is to investigate the best control strategies with minimum cost of implementation as well as financial loss generated. However, the vaccination and effective medicines are the most useful strategies to prevent contagious transmission. The details of each intervention are described as follows:

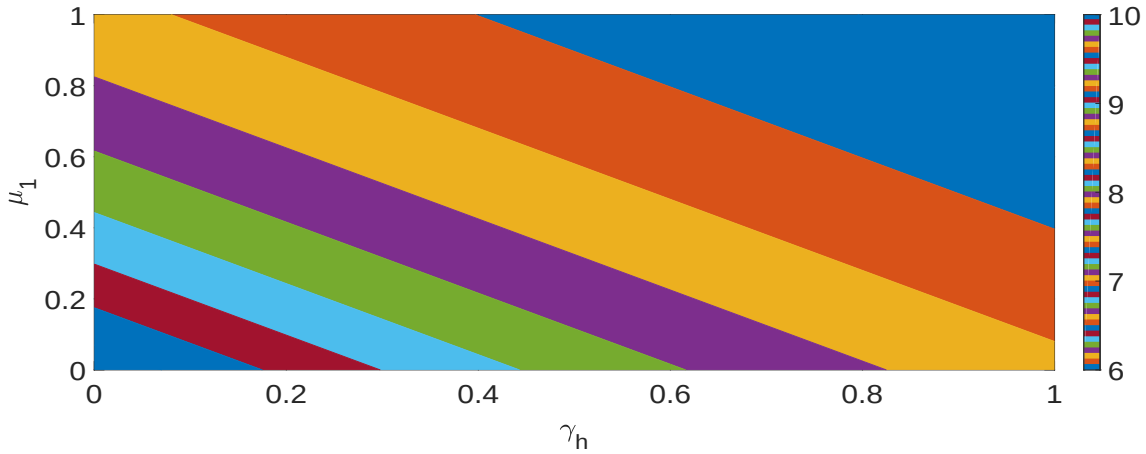
- **Control variable** $u_1(t)$: The force of Japanese Encephalitis infections is reduce by (1-$u_1(t)$), where $u_1(t)$ measures effect due to the use of electronic devices, insecticide-treated bed nets, and mosquito repulsive lotions are used to reduce transmission between mosquitoes and human. If one can reduce between mosquitoes to human transmission rate, then it will be helpful in controlling the mosquito-borne disease. Hence, we consider $u_1(t)$ as a control intervention to reduce human-mosquito interaction.
- **Control variable** $u_2(t)$: The control variable $u_2(t)$ is the pig vaccination lowered the mosquito infection rate. Pig vaccination is associated with a reduction in human cases. In this an effective intervention but requires considerable amount of money. Thus, our main objective is to minimize the disease effect in pig population with minimum cost.
- **Control variable** $u_3(t)$: The control variable $u_3(t)$ is the use of effective medicines for the treatment measure of infectious humans, proper vaccination and insecticide to the Japanese Encephalitis infection causing species [22]. η is the modification parameter



(a)

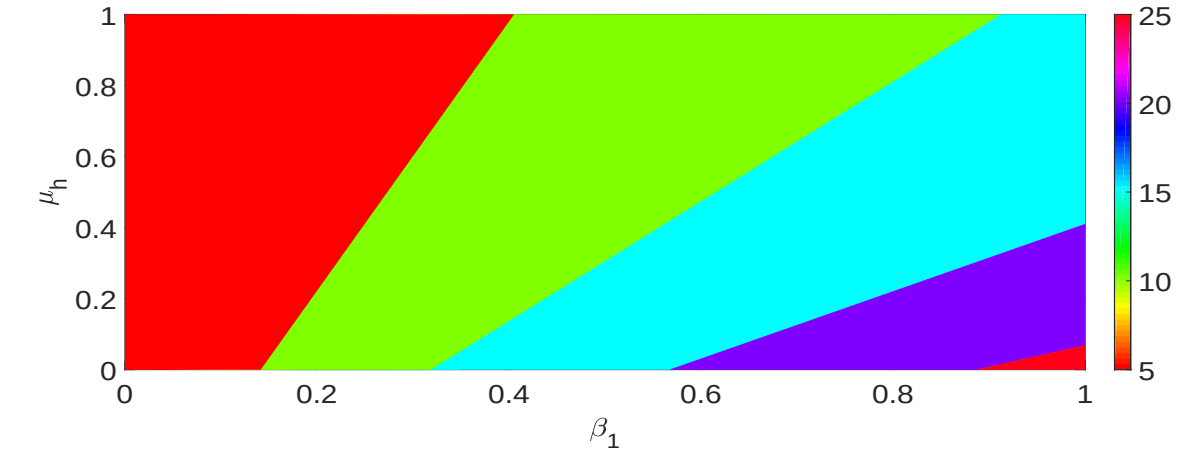


(b)

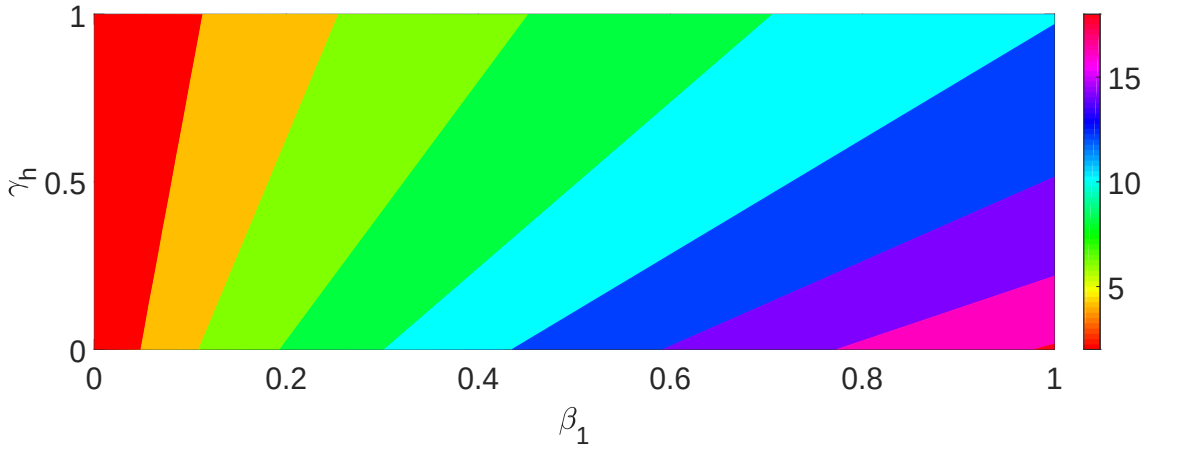


(c)

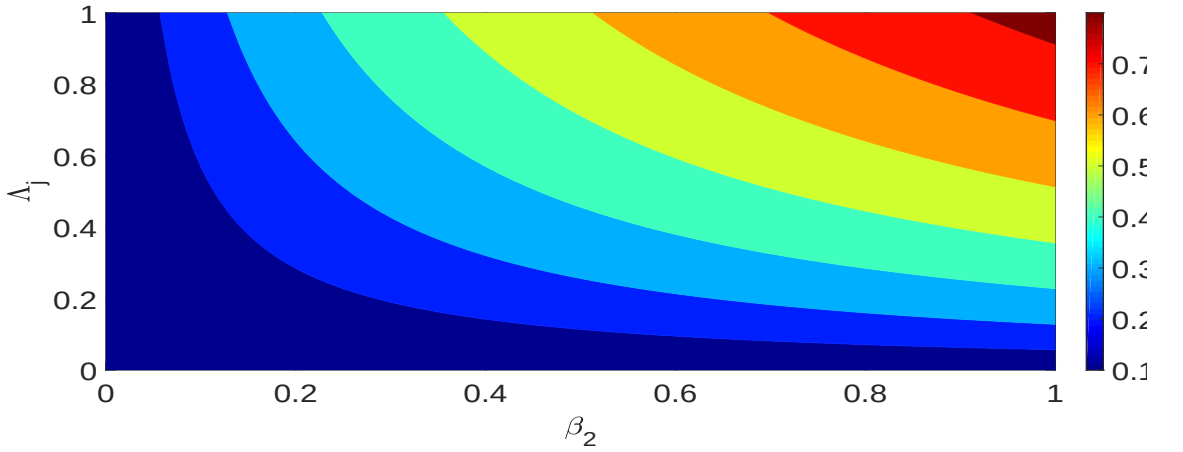
Fig. 5.4. Contour plots of the basic reproduction number $\mathcal{R}_0$ with respect to (a) β_1 and β_2 (b) Λ_j and μ_j, (c) γ_h and μ_1



(a)



(b)



(c)

Fig. 5.5. Contour plots of the basic reproduction number $\mathcal{R}_0$ with respect to (a) β_1 and μ_h, (b) β_1 and γ_h, (c) β_2 and Λ_j

in control $u_3(t)$. In this an effective intervention but requires considerable amount of money. Thus, our main objective is to minimize the disease effect in human population with minimum cost.

Based on different health care restriction , it is essential to impose some bounds on controls as $0 \leq u_1(t), u_2(t), u_3(t) \leq 1$. If $u_1(t)$, $u_2(t)$, and $u_3(t)$ are equal to zero, then there is no effort being placed in these controls at time t and if they are equal to one then the maximum effort is applied. Keeping the view of the above assumptions, the optimal control model is formulated as follows:

$$\begin{cases} \dfrac{dS_h}{dt} = \Lambda_h - (1-u_1(t))\beta_1 S_h \left(\dfrac{I_j}{1+kI_h}\right) - \mu_h S_h + \delta_h R_h \\ \dfrac{dI_h}{dt} = (1-u_1(t))\beta_1 S_h \left(\dfrac{I_j}{1+kI_h}\right) - \dfrac{\eta u_3(t)\gamma_h I_h}{1+\alpha I_h} - (\mu_h+\mu_1) I_h \\ \dfrac{dR_h}{dt} = \dfrac{\eta u_3(t)\gamma_h I_h}{1+\alpha I_h} - (\delta_h+\mu_h) R_h \\ \dfrac{dS_j}{dt} = \Lambda_j - (1-u_1(t))\beta_2 S_j \dfrac{I_h}{N_h} - (1-u_2(t))\beta_3 S_j I_p - \mu_j S_j \\ \dfrac{dI_j}{dt} = (1-u_1(t))\beta_2 S_j \dfrac{I_h}{N_h} + (1-u_2(t))\beta_3 S_j I_p - \mu_j I_j \\ \dfrac{dI_p}{dt} = r I_p \left(1 - \dfrac{I_p}{K}\right) - \mu_p I_p \end{cases} \tag{6.2}$$

Consider $u_1(t) = u_1$, $u_2(t) = u_2$, and $u_3(t) = u_3$ for further analysis.

6.1. Cost Construction and Characterization of Optima Controls

This particular section devotes into two parts which include determination of the total cost generated due to applied controls as well as diseases itself. Whereas the second part determines the analytical forms of the controls.

6.1.1. Total Cost Determination Here, the total cost is determined for the applied control interventions and disease as well, which need to be minimized.

- **Cost due to disease:** The cumulative cost incurred due to the disease burden is modeled as follows:
$$\int_0^T (X_1 I_h + X_2(S_j + I_j) + X_3 I_p) dt$$
This cost consists of various components such as cost due to loss of manpower, opportunity loss and other related wealth loss.
- **Cost incurred in insecticide-treated bed nets:** The total cost involved in reducing the transmission between human to mosquito is given as
$$\int_0^T Y_1 u_1^2 dt.$$
- **Cost incurred intreatment and vaccination for pig population:** The total cost involved in reducing pig infection is defined as
$$\int_0^T Y_2 u_2^2 dt.$$

- **Cost incurred in treatment for infected human population:** The cumulative cost in process of treating infected human is defined by

$$\int_0^T Y_3 u_3^2 dt.$$

The cost functional corresponding to total cost incurred, for fixed time T, which need to be minimized is given by

$$J(u_1, u_2, u_3) = \int_0^T \left[X_1 I_h + X_2(S_j + I_j) + X_3 I_p + \frac{1}{2}(Y_1 u_1^2 + Y_2 u_2^2 + Y_3 u_3^2) \right] dt \quad (6.3)$$

subject to the model system (2).

The parameter $X_1 \geq 0, X_2 \geq 0, Y_1 \geq 0, Y_2 \geq 0$, and $Y_3 \geq 0$, are the weight and balancing constants, which measure the respective cost involvement over the interval $[0, T]$. The term $Y_1 {u_1}^2$ denotes the cost associated with Insecticide-treated bed nets are a form of personal protection that has been shown to reduce mosquito borne disease i.e. zika, dengue, malaria etc. and death due to mosquito borne disease in endemic regions. But at the same time, the execution of ITNs requires lot of money which is given by the term $Y_1 u_1^1$ [11]. Also, the total cost incurred in process primarily includes the cost involved in awareness and educational campaigns, cost of required manpower etc. The term $Y_2 {u_2}^2$ signifies the cost associated with pig vaccination to reduce the mosquito infection rate and the term $Y_3 {u_3}^2$ represents the cost associated with treatment for infected human population which primarily medical facilities, Hospitals expenditure, manpower, human vaccination etc [21]. In order to find an optimal control, ${u_1}^*$,${u_2}^*$, and ${u_3}^*$ such that

$$J({u_1}^*, {u_2}^*, {u_3}^*) = \min_{(u_1, u_2, u_3) \in \mathcal{U}} J(u_1, u_2, u_3), \quad (6.4)$$

where $\mathcal{U}$ is the control set and is defined as

$$\mathcal{U} = \{(u_1, u_2, u_3) : 0 \leq u_1, u_2, u_3 \leq 1, \ t \in [0, T]\}$$

Here, all the controls are bounded and measurable.

6.1.2. Existence and Characterization of Optima Controls Here, we shall first establish the existence of such control functions that minimises the cost functional J. The Lagrangian L of this problem is defined as:

$$L(I_h, S_j, I_j, I_p, u_1, u_2, u_3) = X_1 I_h + X_2(S_j + I_j) + X_3 I_p + \frac{1}{2} Y_1 {u_1}^2 + \frac{1}{2} Y_2 u_2^2 + \frac{1}{2} Y_3 u_3^2$$

Now, we shall use Pontryagin's maximum principle [**?**] for necessary conditions for optimal controls system (2). For that by choosing $A = (S_h, I_h, R_h, S_j, I_j, I_p)$, $\mathcal{U} = (u_1, u_2, u_3)$ and $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$, the associated Hamiltonian $\mathcal{H}$ can be written as

$$\mathcal{H}(A, \mathcal{U}, \lambda) = L(I_h, S_j, I_j, I_p, u_1, u_2, u_3) + \lambda_1 \frac{dS_h}{dt} + \lambda_2 \frac{dI_h}{dt} + \lambda_3 \frac{dR_h}{dt} + \lambda_4 \frac{dS_j}{dt} + \lambda_5 \frac{dI_j}{dt} + \lambda_6 \frac{dI_p}{dt} \quad (6.5)$$

Since u_1^*,u_2^*, u_3^* are solutions to the control problem (2), there exists the adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ satisfying the following conditions.

$$\begin{cases} \dfrac{dx}{dt} = \dfrac{\partial H(t, x, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3.\lambda_4, \lambda_5, \lambda_6)}{\partial \lambda} \\ 0 = \dfrac{\partial H(t, x, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3.\lambda_4, \lambda_5, \lambda_6)}{\partial u} \\ \dfrac{d\lambda}{dt} = -\dfrac{\partial H(t, x, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3.\lambda_4, \lambda_5, \lambda_6)}{\partial x} \end{cases} \quad (6.6)$$

Theorem 6.1:
For the objective functional (3) and the control set (6) subject to control system (2) there exists an optimal control $u^* = ({u_1}^*, {u_2}^*, {u_3}^*) \in \mathcal{U}$ *such that*

$$J({u_1}^*, {u_2}^*, {u_3}^*) = \min_{\mathcal{U}} J(u_1, u_2, u_3).$$

Proof
To establish this result, we follow the Theorem 4.1 mentioned in [23] for the existence of optimal controls. As, we have discussed above that all the state variables (population) are bounded for each bounded controls coming from the control set $\mathcal{U}$. Furthermore, Lipschitz condition with respect to state variables is satisfied by the right hand part of the model system (2). The control variable set $\mathcal{U}$ is also convex and closed by the definition and the model system (2) is linear in control variables. The integrand of the function $L = X_1 I_h + X_2(S_j + I_j) + X_3 I_p + \frac{1}{2}Y_1 {u_1}^2 + \frac{1}{2}Y_2 u_2^2 + \frac{1}{2}Y_3 u_3^2$ is convex on the control set $\mathcal{U}$ due to quadratic nature of control variables. Moreover, $L = X_1 I_h + X_2(S_j + I_j) + X_3 I_p + \frac{1}{2}Y_1 {u_1}^2 + \frac{1}{2}Y_2 u_2^2 + \frac{1}{2}Y_3 u_3^2 \geq \frac{1}{2}Y_1 {u_1}^2 + \frac{1}{2}Y_2 u_2^2 + \frac{1}{2}Y_3 u_3^2$. Now consider $c_1 = min(X_1, X_2, X_3) > 0$ and $g(u_1, u_2, u_3) = c_1({u_1}^2 + {u_2}^2 + {u_3}^2)$. Thus, $L \geq g(u_1, u_2, u_3)$ holds true and g is continuous. Also, g satisfies the condition $|(u_1, u_2, u_3)|^{-1} g(u_1, u_2, u_3) \to \infty$ whenever $|(u_1, u_2, u_3)| \to \infty$. Thus, all the conditions for the existence of controls are fulfilled (for more details one can follow [23, 24]. Hence the result. □

Theorem 6.2:
Let u_1^*, u_2^*, u_3^* *be optimal control functions and* $S_h^*, I_h^*, R_h^*, S_j^*, I_j^*, I_p^*$ *are the corresponding state variable of the optimal control problem (2) - (3). Then there exists adjoint variables* $\lambda = (\lambda_i)^T \in \mathbb{R}^6, i = 1, 2, 3, 4, 5, 6$*, which satisfies the following equations :*

$$\begin{cases} \frac{d\lambda_1}{dt} = \mu_h \lambda_1 + (1-u_1)\beta_1 (\frac{I_j}{1+kI_h})(\lambda_1 - \lambda_2) - (1-u_1)\beta_2 \frac{S_j I_h}{N_h^2}(\lambda_4 - \lambda_5) \\ \frac{d\lambda_2}{dt} = -X_1 + (1-u_1)\frac{\beta_1 S_h I_j k}{(1+kI_h)^2}(\lambda_2 - \lambda_3) + \frac{\eta u_3 \gamma_h}{(1+\alpha I_h^2)}(\lambda_2 - \lambda_3) + (\mu_h + \mu_1)\lambda_2 \\ \frac{d\lambda_3}{dt} = \delta_h(\lambda_3 - \lambda_1) + \mu_h \lambda_3 \\ \frac{d\lambda_4}{dt} = -X_2 + \mu_j \lambda_4 + (1-u_1)\beta_2 \frac{I_h}{N_h}(\lambda_4 - \lambda_5) + (1-u_2)\beta_3 I_p(\lambda_4 - \lambda_5) \\ \frac{d\lambda_5}{dt} = -X_2 + (1-u_1)\beta_1 S_h (\frac{1}{1+kI_h})(\lambda_1 - \lambda_2) + \mu_j \lambda_5 \\ \frac{d\lambda_6}{dt} = -X_3 + (\mu_p + r - \frac{2rI_p}{k})\lambda_6 \end{cases} \tag{6.7}$$

with transversality conditions

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = 0 \tag{6.8}$$

Proof
Let u_1^*, u_2^*, u_3^* be the optimal control functions and $S_h^*, I_h^*, R_h^*, S_j^*, I_j^*, I_p^*$ are the corresponding state variables. Then, Pontryagin's Maximum Principle ensures the existence of the following adjoint variable $\lambda_i (i = 1, 2, 3, 4, 5, 6) \in \mathbb{R}^6$, which satisfies the following canonical equations:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_h}, \ \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I_h}, \ \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial R_h}, \ \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial S_j}, \ \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial I_j}, \ \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial I_p}$$

with transversality conditions (8), where $\mathcal{H}$ is the Hamiltonian defined as above. Thus, the adjoint system (7) can be obtained, □

In the following result, we shall state the analytical forms of the optimal controls.

Theorem 6.3:
The optimal controls $(u_1{}^*, u_2{}^*, u_3{}^*)$ *which minimizes J over the region* $\mathcal{U}$ *given by*

$$u_1{}^* = min\{1, max(0, \widetilde{u_1})\}$$
$$u_2{}^* = min\{1, max(0, \widetilde{u_2})\}$$
$$u_3{}^* = min\{1, max(0, \widetilde{u_3})\}$$

where,

$$\begin{aligned} \widetilde{u_1} &= \frac{\beta_1 \left(\frac{S_h + I_j}{1 + kI_h}\right)(\lambda_2 - \lambda_1) + \frac{\beta_1 S_h I_j k}{(1 + kI_h)^2}(\lambda_3 - \lambda_2) + \beta_2 \frac{I_h}{N_h}(\lambda_5 - \lambda_4)}{Y_1} \\ \widetilde{u_2} &= \frac{\beta_3 I_p(\lambda_5 - \lambda_4)}{Y_2} \\ \widetilde{u_3} &= \frac{\frac{\eta\gamma_h}{(1 + \alpha I_h^2)}(\lambda_3 - \lambda_2)}{Y_3} \end{aligned} \tag{6.9}$$

Proof
Using the optimal condition (6), we get (9), as follows

$$\frac{\partial \mathcal{H}}{\partial u_1} = Y_1 u_1 + \beta_1 \left(\frac{S_h + I_j}{1 + kI_h}\right)(\lambda_1 - \lambda_2) + \frac{\beta_1 S_h I_j k}{(1 + kI_h)^2}(\lambda_2 - \lambda_3) + \beta_2 \frac{I_h}{N_h}(\lambda_4 - \lambda_5) = 0$$

This implies,

$$u_1 = \frac{\beta_1 \left(\frac{S_h + I_j}{1 + kI_h}\right)(\lambda_2 - \lambda_1) + \frac{\beta_1 S_h I_j k}{(1 + kI_h)^2}(\lambda_3 - \lambda_2) + \beta_2 \frac{I_h}{N_h}(\lambda_5 - \lambda_4)}{Y_1} := \widetilde{u_1},$$

$$\frac{\partial \mathcal{H}}{\partial u_2} = Y_2 u_2 + \beta_3 I_p(\lambda_4 - \lambda_5) = 0$$

This implies,

$$u_2 = \frac{\beta_3 I_p(\lambda_5 - \lambda_4)}{Y_2} := \widetilde{u_2},$$

And,

$$\frac{\partial \mathcal{H}}{\partial u_3} = Y_3 u_3 + \frac{\eta\gamma_h}{(1 + \alpha I_h^2)}(\lambda_2 - \lambda_3) = 0$$

This implies,

$$u_3 = \frac{\frac{\eta\gamma_h}{(1 + \alpha I_h^2)}(\lambda_3 - \lambda_2)}{Y_3} := \widetilde{u_3}.$$

Moreover, lower and upper bounds of these control are 0 and 1 respectively. Thus, if $\widetilde{u_1} > 1,\ \widetilde{u_2} > 1,\ \widetilde{u_3} > 1$, then

$$u_1 = u_2 = u_3 = 1.$$

Also, $\widetilde{u_1} < 0,\ \ \widetilde{u_2} < 0\ \ , \widetilde{u_3} < 0$, then

$$u_1 = u_2 = u_3 = 0.$$

Otherwise, we have

$$u_1 = \widetilde{u_1},\ \ u_2 = \widetilde{u_2},\ \ and\ \ u_3 = \widetilde{u_3}$$

Hence, for these controls $u_1^*,\ u_2^*,\ u_3^*$ we get optimum value of the function J. □

7. SIMULATION OF OPTIMAL CONTROL

In this section, by using MATLAB software, the optimal control model is simulated. The parameter values are remain same as esteemed in the Table 1. The weight constants for the optimal control problem are taken as $X_1 = 1, X_2 = 1, X_3 = 1, Y_1 = 45, Y_4 = 65, Y_5 = 75$. We solve the optimality system (2) by iterative method with the help of forward and backward difference approximations [23]. We consider the time interval as [0, 200]. Profiles for optimal control u_1,u_2 and u_3 are shown, respectively, in Figures 6(a), 6(b), and 6(c). Finally, to see the effects of optimal controls, the infected human and infected vectors are plotted against time with and without optimal control in Figures 7(b). It is easy to notice that optimal control is more effective in reducing the number of infectives. We consider different types of strategies to see the impact of optimal control in the total number of human infectives. For this purpose, we shall define the following control strategies:

- Strategy A: Employing control intervention (u_1), only.
- Strategy B: Employing control intervention (u_2) only.
- Strategy C: Employing control intervention (u_2) only.
- Strategy D: Employing control intervention $(u_1, u_2), (u_1, u_3), (u_2, u_3)$
- Strategy E: Employing control intervention (u_1, u_2, u_3)

7.1. Strategy A: Employing electronic devices, insecticide-treated bed nets, and mosquito repulsive lotions (u_1), only.

Here, only control measure $u_1(t)$ is used to optimize the objective function J, while control intervention $u_2(t) = u_3(t) = 0$, were not employed. The influence of $u_1(t)$ is demonstrated in Figure 6(a), to minimize the objective function, the optimal control $u_1(t)$ is maintained at the maximum level. A single preventive measure can influence the spread of Japanese Encephalitis in the population.

7.2. Strategy B: Increase pig vaccination to reduce the mosquito infection (u_2) only.

Here, only control measure $u_2(t)$ is used to optimize the objective function J, while control intervention $u_1(t) = u_3(t) = 0$, were not employed. In Figure 6(b), we present the plots of population and the due to effects of pig vaccination are demonstrated to minimizing the cost and reducing the number of Japanese Encephalitis infections in the population.

7.3. Strategy C: Use of effective medicines as treatment measure of infectious humans (u_3) only.

Here, only control measure $u_3(t)$ is used to optimize the objective function J, while control intervention $u_2(t) = u_3(t) = 0$, were not employed. The influence of $u_3(t)$ is demonstrated in Figure 6(c), to minimize the disease effect in human population with minimum cost.

7.4. Strategy D: Effective use of control intervention $(u_1, u_2), (u_1, u_3), (u_2, u_3)$.

Here, double control interventions $(u_1(t), u_2(t))$ when $u_3(t) = 0$, $(u_1(t), u_3(t))$ when $u_2(t) = 0$, and $(u_2(t), u_3(t))$ when $u_1(t) = 0$, are used to optimize the objective function J.

The control intervention are demonstrated in Figure 6(d), 6(e) and 6(f). It is observed that combination of two control intervention is most effective then using signal control intervention. Significant number of Japanese Encephalitis infective cases reduce.

7.5. Strategy E: Employing all three control interventions (u_1, u_2, u_3).

Here all three control interventions $(u_1(t), u_2(t), u_3(t))$ are used to optimize the objective function J. From Figure 7(a), it is easy to say that by combining all three optimal controls $u_1(t)$, $u_2(t)$, and $u_3(t)$, the total number of infectious individuals decreases significantly. The three optimal control application is the best control strategy to minimize the number of infectives, and will definitely reduce the spread of JEV.

8. CONCLUSION

In this study, a non-linear mathematical model is formulated and analyzed for Japanese encephalitis disease with saturated incident $\left(\frac{\beta_1 S_h I_j}{1+kI_h}\right)$ and saturated treatment function $\left(\frac{\gamma_h I_h}{1+\alpha I_h}\right)$. The basic reproduction number is computed by next generation matrix method. Here, it is clearly identify that the parameter β_1 is the most sensitive parameter which transmitted Japanese encephalitis disease in human. The sensitivity analysis of the basic reproduction and Japanese encephalitis infected cases are executed in order to determine the relative importance of the model parameters to the disease prevalence. The results of the numerical simulation is executed to support our mathematical findings and demonstrated graphically. Also, we perform here trend of Japanese encephalitis cases of Assam and Uttar Pradesh through line-graph. The infection rate is high in Assam and Uttar Pradesh comparatively other part of the country(India). Three time-department optimal control is incorporated in model system to eliminate the virus from the tropical region using Pontryagin's maximum principal. Adapting all three optimal control parameters are the best control strategy to minimize the number of infectives, which will reduce the rate transmission of the disease. It is noticed easily that use optimal control in the mode is more effective than without optimal control in reducing the number of infectives in the considered period.

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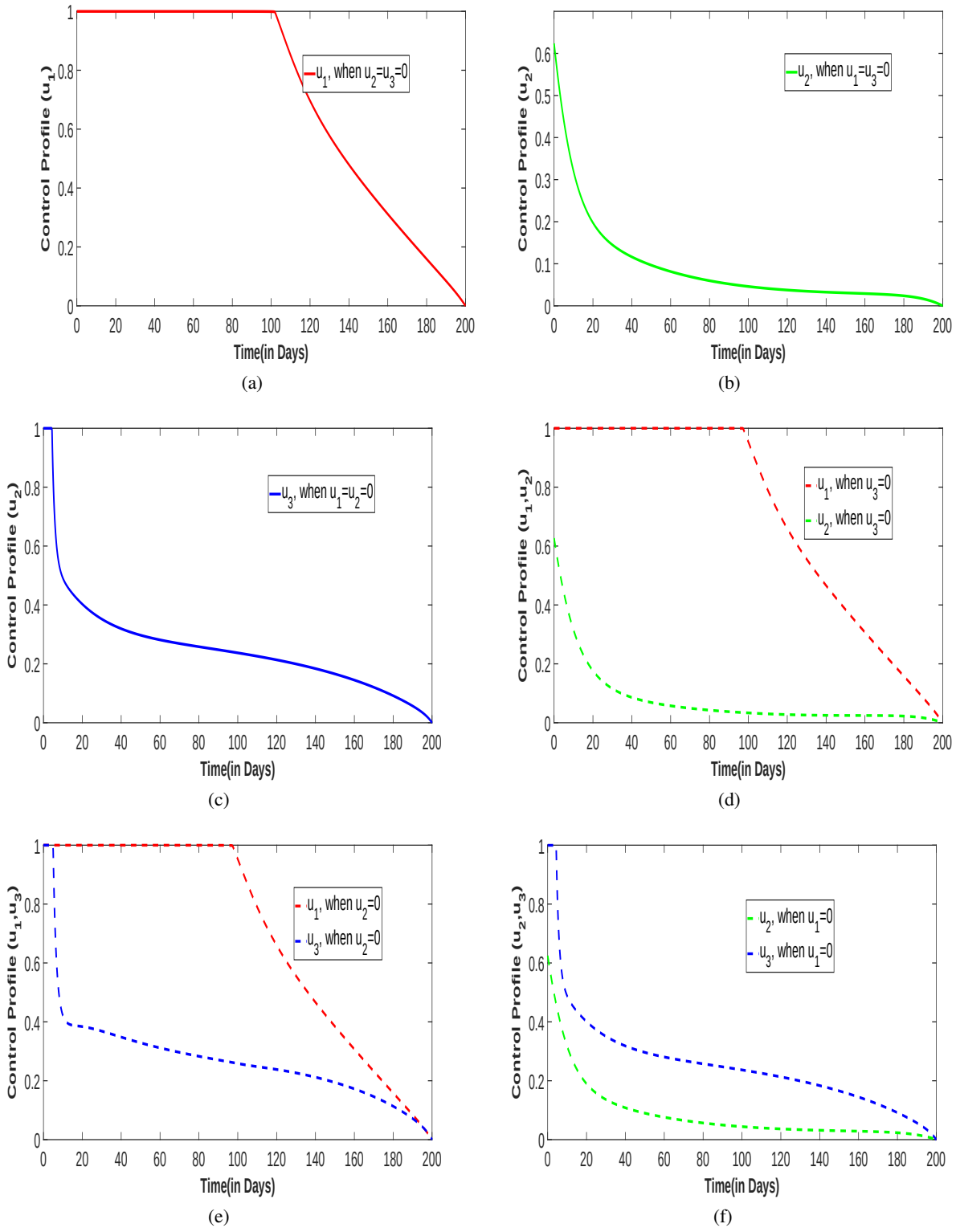
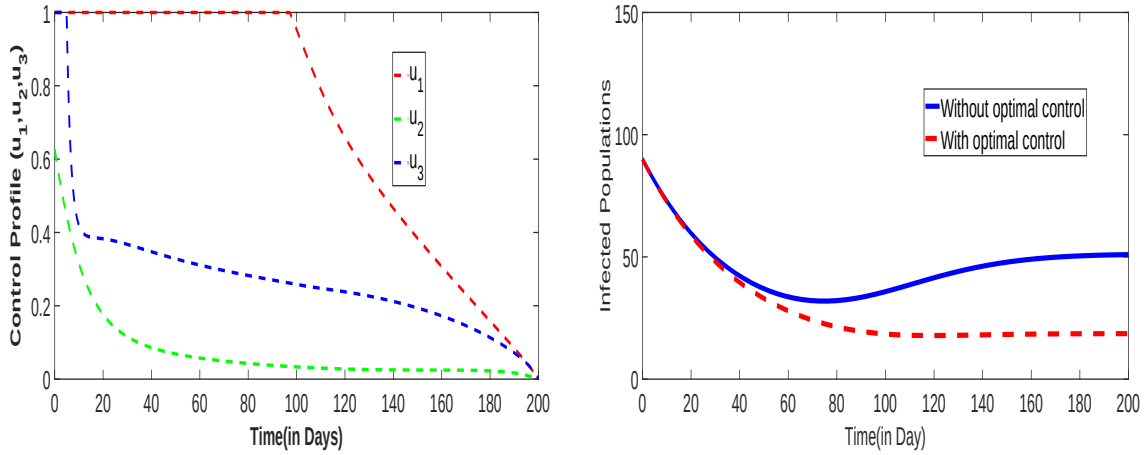


Fig. 7.6. (a) Control profile of u_1, when $u_2 = u_3 = 0$, (b) Control profile of u_2, when $u_1 = u_3 = 0$, (c) Control profile of u_3, when $u_2 = u_3 = 0$, (d) Control profile of u_1, u_2, when $u_3 = 0$,(e) Control profile of u_1, u_3, when $u_2 = 0$, (f) Control profile of u_2, u_3, when $u_1 = 0$



(a) (b)

Fig. 7.7. (a) Control profile of u_1, u_2, and u_3, (b) Variation of infected human populations against time with and without optimal control.

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