Host Pathogen Interactions: Insight of Delay Response Recovery and Optimal Control in Disease Pathogenesis

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Abstract— **Research in the infection and recovery, based on mathematical understanding is aimed at developing how the immune system protects against infectious diseases, with a major focus on host-pathogen interactions [1]. In recent years greatest challenges in front of humanity is learning how the immune response protects against variety of breathing and emerging infectious disease. A lot of theoretical and experimental investigations of natural selections in host-pathogen system been explored and it has been established that vaccination is the most cost effective public health tool in human history [2]. In this research articles we attempt to offers an opportunity to examine the mathematical relationship that forming a model between host and pathogen as in biology and manifests the time rate of change of these species for better understanding of the recovery of the disease. On that outlook a recovery rate of the infected host to that of susceptible host is incorporated in our proposed mathematical model. Then we introduce a discrete time delay to the model to describe the time requirement for recovery from infected host to susceptible host by using various drugs or vaccinations. Again we use optimal control that is characterized in terms of the optimality of the system, to achieve improved quality of treatment. The model is analyzed theoretically and numerically. Numerical solution of the model is in conformity with those obtained theoretically. An effort is made to relate the model to prototype biological system by exploring a probable disease free parametric region. We also studied the effect of time delay on the stability of the infected equilibrium and optimal control process which can reduce the infected host populations.**

Keywords: *Host Pathogen, Mathematical models, Time Series Solutions, Asymptotic Stability, Delay, Recovery, Optimal Control, Numerical Solutions.*

1 Introduction

Mathematics explores the language of science and technology. Its application in theoretical biology has become immense important in analyzing the spread and control of infectious disease. So far mathematical analysis carried through modelling of biological process is enormously useful in treatment of disease, various detection, and prevention therapy and control programs by using a variety of mathematical tools and techniques [3], [4] [5], [6], [7], [8], [9], [10], [11], [12]. In that sense differential equations could be used potentially to understand epidemiological systems in order to contain the outbreak of epidemiological diseases, which was considered initially by Ronald Ross way back in 1911 [13]. By using a set of differential equation Sir Ross understood that a certain thresholds relating to malarial eruption within the species Homo sapiens was helped him greatly towards discovering malaria vaccine. A incredible assortment of models have been formulated using mathematical perception and method, to analyze epidemiological or such class of biological systems specially when infectious disease are involved in the system. These models have involved aspects such as passive immunity, general loss of vaccine and disease-acquired immunity, stages of infection, vertical transmission, disease vectors, macroparasite loads, age structure, spatial spread, vaccination quarantine, chemotherapy, etc. [14], [15]. It would be mentioned here that Hammer (1906) [16] formulated and analyzed a discrete time delay model to understand the recurrence of measles epidemics. Daniel Bernoulli (1970) started the pioneering venture of applying mathematical concepts in case of epidemics like small pox. Not only has that, these special models been formulated as disease such as rubella, chickenpox, whooping cough, rabies, diphtheria, filariasis, rabies, gonorrhoea, herpes, syphilis, and HIV/AIDS for enrich understanding of biological system [14].

Over that last few years microbiologist tried to introduce the thought of the term host-pathogen interaction [17], [18], [19], that microbial pathogenesis reflects an interaction between two entities host and pathogen [20]. From that point of view of disease pathogenesis, the interaction is reducible into two outcomes: those that result in damage to the host and those that result in no damage. Disease occurs when the host sustains sufficient damage to perturb homeostasis [21], [22]. With an idea of that host damage or no damage is the most pertinent consequence of the host-pathogen interaction. In a biological or immunological system when we considering disease eruption, the ultimate apprehension of our researcher is to count actual amount of damage through potentially seri-

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ous pathogens which will be depend upon the virulence of pathogen-host interaction by any means research work [23]. Now we are going to able discuss about host-pathogen models which are mathematically prototypes pertaining to epidemiology and these are in immense important in view of the emergence and re-emergence of epidemiological disease in the present day of global scenario. In this type of model the host population is divided into two classes, susceptible (S) i.e., healthy organisms and infected individuals (I). Pathogens (V) cause infection to host transforming S to I. The model actually describes the time rate of change of S, I, and V including various realistic model parameters arising out of influence from environment, immunization, inter-class contact etc. These classes of models are important in their own rights and are also relevant for predator-prey or host-parasite type of models. In the predator-prey models, the effect of pathogenic diseases on the model dynamics and its constituents is an important area from mathematical as well as ecological point of view. Thus researchers are paying increased attention to the entire spectrum of host-pathogen research from recent novel insight into innate immunity to the pathogenesis of major global pandemics, such as HIV, TB, malaria and pathogenesis of emerging infections such as SARS and hemorrhagic fevers [2], [24], [25].

Now we look into the sequence of historical events relating to host-pathogen interactions with enormous ideas of biological as well as mathematical research for recent years. Though earlier we have mentioned the work of Arturo and Liise [20], [21] where they signifies their ideas that host-pathogen interactions can be analyzed using host damage as the common denominator for characterizing microbial pathogenecity and can provide a conceptual frame work for incorporating the importance of the host response into the outcome of the host microbe interaction. They have also established that the measures of damage that rely on mortality, tissue destruction, or clinical disease may be too intensive to characterize host-pathogen interactions that lead to colonization or chronicity. Roy and Chattopadhyay [1] focused in their recent works on three species mathematical model of host-pathogen interactions that the removal of infected host population is caused by the biological and physical realizable threshold of recovery rate. Chattopadhyay, Mukhopadhyay and Roy [26] took a generalized Gause model of prey-predator character including viral infection and studied the stability of the different populations. Hethcote and Driessche [27] formulated SIS epidemiologic models where delay has been incorporated corresponding to the infectious period, and disease related deaths. They have shown that the model with logistic dynamics, periodic solutions in the infectious fraction can occur as the population approaches extinction for a small set of parameter values. Furthermore another pioneer work carried out by Ennos [23] where he has drawn his attention that the transport of co-evolved pathogen-host systems into new environment may lead to the evolution of altered levels of pathogen aggressiveness, if transmission rates are different in the new environment. With the growing research in the prey-predator and other prototypical systems, it became apparent that, the pathogen or viral growth through replication influences the model dynamics. Bairagi, Roy and Chattopadhyay [28] emphasized the same in a subsequent communication. Bairagi, Roy and Chattopadhyay [29] in their pioneer communication

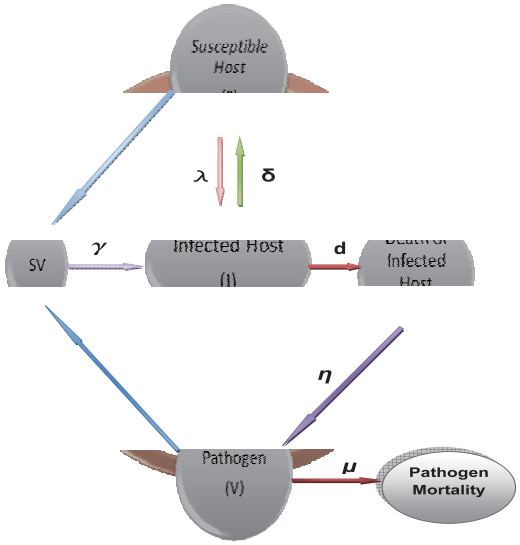

Figure 1: Schematic diagram of the model system equations(2.6) depicting the inter flow of constituent populations.

in recent years, carried a comparative study of a predator-prey model with several response function. More recently Stengel [30] examine through a set of differential equations forming by a wild-type model of host pathogen and also the mutant infection. His study shows that current drug class can provide indirect control of low fitness drug-resistant HIV strains through dynamic coupling to wild-type strains and immune system dynamics. From computational analysis he conclude that "hit early, hit hard" therapy is optimal, derived from clinical experience.

In this paper we consider a conventional host-pathogen model including a recovery of the infected individuals to the healthy organisms termed as susceptible [1]. The essential features of a conventional host pathogen system such as, logistic growth of susceptible, pathogen replication, lysis death of infected individuals and mortality of pathogens, are all incorporated in the model. We would predominantly explore the bearing of host recovery on the stability of the system and related characteristics.

In this paper we also propose and analyze mathematical model of host-pathogen interactions, assuming infected hosts which do not grow or reproduce but they can recover from pathogenic infection and move to add to the susceptible host population and this recovery would stem out from immunization or vaccination. Thus there exists a finite time lag or delay in the process of recovery and this finite time lag exist between actively infected host and getting its subsequent recovery. Such realistic time lag has been incorporated in the model under consideration. In this case our aim is to study the dynamics of the proposed model including delay and to explore the crucial system parameters and their ranges in order to obtain different theoretical behaviors predicted from the inter-

action between susceptible host, infected host and pathogen, and moreover the recovery response against pathogen infected host population through immunization or vaccination.

In *section 4* of our research article we have used an optimal control theory paradigm to host-pathogen interactions model with therapeutic outlook and such therapeutic control as a way to suppress the pathogenic production. Our analytical and numerical results reveal that how a cost-effective combination of treatment efforts may depend on the population size, cost of implementing treatments control and the different parameters of the model.

The model is analyzed in two different avenues, analytical and numerical. Coupled differential equations depicting the model system are made dimensionless and the linearized fixed point solutions of these equations are obtained. Existence, uniqueness and boundedness of the non trivial fixed point solutions are checked. Stability of the system is analyzed and conditions are obtained. In *section 3* of our research article we have find out Sufficient Conditions for Nonexistence of Delay Induced Instability and Criterion for Preservation of Stability,Instability and Bifurcation Results. Lastly we have find out Optimally Controlling Therapy. Model equations are solved numerically to check threshold values of different model parameters and the concurrence of these solutions with those obtained analytically are checked. Numerical findings are in agreement with the theoretical results.

2 The Basic Assumptions and the Mathematical Model

We consider a host pathogen model consisting of a host population, whose concentration is denoted by N ($[N]$ = number of host per designated area) and a pathogen population inflicting infection in the host population whose concentration is denoted by V ($[V]$ = number of pathogens per designated area). In the presence of pathogenic infection, the host population is divided into two disjoint classes, susceptible S, and infected I.

The following assumptions are made to formulate the basic model equations.

(A1): In the ideal case of no pathogen the growth of susceptible host population follows the logistic law [6] implying that this growth is entirely controlled by an intrinsic birth rate constant $r(\in R_+)$ with a carrying capacity $K(\in R_+)$. The mathematical form of such logistic growth is

$$\frac{dN}{dt} = rN(1 - \frac{N}{K}). \tag{2.1}$$

(A2): Introduction of pathogen in the system splits the host population into two disjoint classes, namely susceptible host S and infected host I, such that at any time t the total host population remains as

$$N(t) = S(t) + I(t). \tag{2.2}$$

(A3): S increases its population by reproduction as per logistic law (2.1), but I are incapable of any reproduction [6].

(A4): At any instant of time, all susceptible host population (S) are equally susceptible and all infected population are equally infectious.

(A5): It is assumed that the spread of disease takes place in two avenues namely, by pathogens as well as by contact of a susceptible host with a infected host. Pathogens are maximally infect γ susceptible hosts per day. This infection rate is half maximal at susceptible host population density of h_γ host.

It should be noted here that some researchers argued in favor of proportional mixing rate of contact between S and I rather than a simple law of mass action. But Greenwood experiment [4] on prototype systems showed that quantitative results remain the same in either cases of the mentioned contact processes.

Following assumptions (A3), (A4) and (A5), equation (2.1) can be written as

$$\frac{dS}{dt} = rS(1 - \frac{S+I}{K}) - \lambda SI - \frac{\gamma SV}{h_\gamma + S} \tag{2.3}$$

where $\lambda(\in R_+)$ is the intensity of infection by infected host and and $\gamma(\in R_+)$ is the force of infection through contact with pathogens.

The equation depicting the dynamics of pathogen population thus becomes

$$\frac{dV}{dt} = -\frac{\gamma SV}{h_\gamma + S} + \eta dI - \mu V \tag{2.4}$$

where $d(\in R_+)$ is the death rate constant of I. Note that we consider the mortality of I to be completely due to lysis and there exists no separate base line mortality of it. Here $\eta(\in R_+)$ is the rate of cell lysis (replication of pathogens) and the natural death rate of pathogens is denoted as $\mu(\in R_+)$.

Based on the string of arguments the time rate of change of I can be written as

$$\frac{dI}{dt} = \lambda SI + \frac{\gamma SV}{h_\gamma + S} - dI. \tag{2.5}$$

(A6): We assume that the infected hosts do not grow or reproduce but they can recover from pathogenic infection and move to add to the susceptible host population. Such recovery would stem out from immunization or vaccination. We consider a recovery rate of I to be denoted by $\delta(\in R_+)$.

Following the above assumption $(A1 - A6)$, the final set of equations depicting the dynamics of susceptible host, infected host and pathogens can be written as

$$\begin{aligned} \frac{dS}{dt} &= rS(1 - \frac{S+I}{K}) - \lambda SI - \frac{\gamma SV}{h_\gamma + S} + \delta I \\ \frac{dI}{dt} &= \lambda SI + \frac{\gamma SV}{h_\gamma + S} - dI - \delta I \\ \frac{dV}{dt} &= -\frac{\gamma SV}{h_\gamma + S} + \eta dI - \mu V \end{aligned} \tag{2.6}$$

where, $S(0) > 0, \;\; I(0) > 0, \quad V(0) > 0.$

The set of equations (2.6) constitute a generalized mathematical model for host-pathogen. A schematic diagram showing the flow of different constituent masses of host and pathogens conforming to the mathematical equations (2.6) . The variables of model equations (2.6) are to be made dimensionless for the sake of simplicity. Here we rescale all the variables in

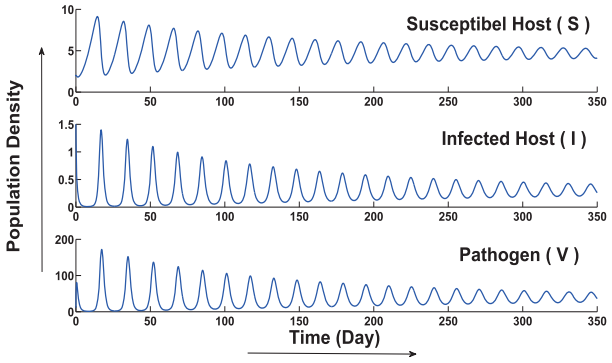

Figure 2: Population densities of Susceptible host (S), Infected host (I) and Pathogen (V) are plotted as a function of time for the Recovery rate $\delta = 0.2$. Other parameters are as in Table.1.

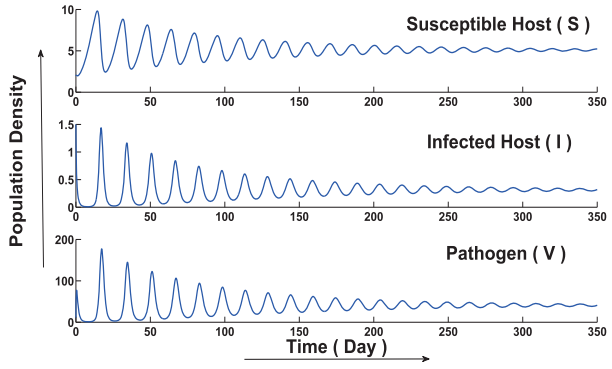

Figure 3: Population densities of Susceptible host (S), Infected host (I) and Pathogen (V) are plotted as a function of time for the Recovery rate $\delta = 0.4$. Other parameters are as in Table.1.

terms of carrying capacity K. Thus we apply the transformation, $s = \frac{S}{K}, i = \frac{I}{K}, v = \frac{V}{K}, \tau = rt$ and get the following dimensionless form of the model equation (2.6). For notational convenience we will replace τ by t henceforth. The rescaled equations are

$$\begin{array}{l} \frac{ds}{dt} = s(1-(s+i)) - asi - \frac{bsv}{c+s} + mi \\ \frac{di}{dt} = asi + \frac{bsv}{c+s} - fi - mi \\ \frac{dv}{dt} = -\frac{bsv}{c+s} + gi - hv \end{array} \tag{2.7}$$

where, $a = \frac{\lambda K}{r}$, $b = \frac{\gamma K^2}{r}$, $c = \frac{h\gamma}{r}$, $m = \frac{\delta}{r}$, $f = \frac{d}{r}$, $g = \frac{\eta d}{r}$, and $h = \frac{\mu}{r}$.

2.1 Existence, Uniqueness and Boundedness

We observe that right hand side of equation (2.7) are smooth functions of the variables s, i, v and parameters, as long as these quantities are non-negative, so local existence and uniqueness properties hold in the positive octant for some time interval $(0, t_f)$. In the next theorem we show that the linear combination of susceptible host, infected host and pathogens is less than a finite quantity or in other words, the solution of the system (2.7) is bounded.

Theorem 2.1 *All the solution $y(t)$ of (2.7), where $y = (s, i, v)$, is uniformly bounded for $y_0 \in R^3_{0,+}$.*

Proof: We define a function $W(t) : R_{0,+} \to R_{0,+}$ by

$$W(t) = s + i + v. \tag{2.1.1}$$

Observe that W is well defined and differentiable on some maximal interval $(0, t_f)$

The time derivative of (2.1.1) along the solutions of (2.7) is

$\frac{dW(t)}{dt} = (s+i)(1-s-i) - fi - \frac{bsv}{c+s} + gi - hv,$
i.e., $\frac{dW(t)}{dt} \leq (s-1)^2 - s - (f-g)i - hv + 1$

If we assume that, $0 < \varrho < min.(1, f-g, h)$ then we get $\frac{dW(t)}{dt} + \varrho \leq 1$ for each $t \in (0, t_f)$.

Applying the theory of differential inequality [5] we obtain, $0 < W(s,i,v) < \frac{1}{\varrho}(1-e^{-\varrho t}) + W(s(0), i(0), v(0))e^{-\varrho t}$, and for $t \to \infty$, we have

$$0 < W < \frac{1}{\varrho}. \tag{2.1.2}$$

Hence all the solutions of $y(t)$ that initiate in R^3_+ are confined in the region $\widehat{B} = \{(s,i,v) \in R^3_+ : W = \frac{1}{\varrho} + \kappa, \quad for\ any\ \kappa > 0\}$. Hence the proof.

2.2 Equilibria Conditions

System (2.7) possesses the following equilibria: $E_0(0,0,0)$, $E_1(1,0,0)$, and $E^*(s^*, i^*, v^*)$

where, $i^* = \frac{s^*(1-s^*)}{S^*+f}$, $v^* = \frac{gi^*(s^*+c)}{bs^*+h(s^*+c)}$ and s^* is the positive root of

$$\Omega_1 (s^*)^2 - \Omega_2 s^* - \Omega_3 = 0 \tag{2.2.1}$$

and $\Omega_1 = ab + ah$, $\Omega_2 = bf + hf + bm + mh - bg - ach$ and $\Omega_3 = (m+f)ch$. Note that equation (2.2.1) has a unique positive root, given by $s^* = \frac{\Omega_2 + \sqrt{\Omega_2^2 + 4\Omega_1\ \Omega_3}}{2\Omega_1}$, if $\Omega_1 > 0$, $\Omega_2 > 0$ and $\Omega_3 > 0$ for which $(b+h)(m+f) > (gb + ach)$. It is to be noted here that

$$s^* + i^* \leq 1. \tag{2.2.2}$$

This condition is due to the fact that $s(t) + i(t) \leq 1, \forall\ t > 0$.

2.3 Stability Analysis

Constructing the variational matrix about any arbitrary equilibrium $E(s,i,v)$, we state and prove the following theorems:

Theorem 2.3.1 The system (2.7) is unstable around E_0 for all parametric values. (The proof is obvious).

Theorem 2.3.2 The system (2.7) is asymptotically stable around E_1 if $a + \frac{gb}{b+h(1+c)} < (m+f)$.

Proof: The variational matrix corresponding to E_1 is

$$\begin{pmatrix} -1 & -1-a+m & \frac{-b}{1+c} \\ 0 & a-m-f & \frac{b}{1+c} \\ 0 & g & \frac{-b}{1+c} - h \end{pmatrix} \tag{2.3.1}$$

The eigenvalue of the variational matrix corresponding to equilibrium E_1 is

$$\chi = -1 \quad and \quad \chi^2 - \vartheta_1 \chi - \vartheta_2 = 0 \tag{2.3.2}$$

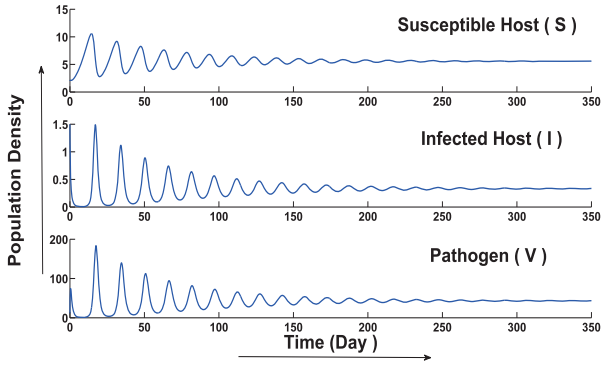

Figure 4: Population densities of Susceptible host (S), Infected host (I) and Pathogen (V) are plotted as a function of time for the Recovery rate $\delta = 0.6$. Other parameters are as in Table.1.

where, $\vartheta_1 = a - m - f - h - \frac{b}{1+c}$ and $\vartheta_2 = (a - m - f)(h + \frac{b}{1+c}) + \frac{gb}{1+c}$. The last equation of (2.3.2) containing two eigenvalues implies that it has two roots and it is obvious that the system (2.7) is asymptotically stable around E_1 if $a + \frac{gb}{b+h(1+c)} < (m + f)$.

Theorem 2.3.3 The system (2.7) is always stable around E^* for all parametric values if

(i) $max(\frac{m+f}{2}, \frac{m+f}{a}) < s^* < min(\frac{f}{a(1+a)}, \frac{f^2}{m+f+g}, 2g)$,
(ii) $max(3as^*, 2g, \frac{g}{a}, \frac{g^2}{v^*}, \frac{a^2}{4}, \frac{g(1+a)}{a^2}, \frac{abs^*}{v^*}) < f < \frac{g^2}{2(1+g)}$,
(iii) $min(\frac{2f}{g+f}, \frac{f}{f+g}) > a$,
(iv) $m > max(\frac{g}{s^*}, \frac{2f+1}{g}, 2(1+g))$,
(v) $c > \frac{m+f}{s^*}$, (vi) $i^* > \frac{1+g}{1+a}$.

Proof: Observe that from first two equations of the system (2.7), we always have

$$\frac{d(s+i)}{dt} = (s+i)(1-(s+i)) - fi < (s+i)(1-(s+i)).$$

Hence [32] we have $\lim_{t\to\infty} \{s(t) + i(t)\} < 1$. Thus we have $s^* + i^* < 1$ and the last condition (2.2.1) is always satisfied.

The characteristic equation of the linearized system of (2.7), corresponding to E_*, is given by

$$\xi^3 + A_2\xi^2 + A_1\xi + A_0 = 0. \tag{2.3.3}$$

Where,

$$\begin{aligned} A_2 &= 2s^* + i^* - 1 - g + m + f - as^* + ai^* + \tfrac{bcv^*}{(s^*+c)^2}, \\ A_1 &= +\tfrac{bcfv^*}{(s^*+c)^2} + \tfrac{bcs^*v^*}{(s^*+c)^2} + \tfrac{ag(i^*)^2}{v^*} + afi^* + +g - gi^* \\ &\quad - 2gs^* - m + mi^* + 2ms^* - f + fi^* + 2fs^* \\ &\quad + as^* - 2a(s^*)^2 + \tfrac{g^2i^*}{v^*} + \tfrac{fgi^*}{v^*} + \tfrac{gmi^*}{v^*} - \tfrac{ags^*i^*}{v^*}, \\ A_0 &= \tfrac{ags^*i^*}{v^*} - \tfrac{2g(s^*)^2i^*}{v^*} + \tfrac{2fgs^*i^*}{v^*} + \tfrac{afg(i^*)^2}{v^*} \\ &\quad + \tfrac{fg(i^*)^2}{v^*} - \tfrac{g^2(i^*)^2}{v^*} - \tfrac{gm(i^*)^2}{v^*} + \tfrac{2gms^*i^*}{v^*} - \tfrac{mgi^*}{v^*} \\ &\quad + \tfrac{gi^*}{v^*} - \tfrac{fgi^*}{v^*} + \tfrac{mg(i^*)^2}{v^*} + \tfrac{bchv^*}{(s^*+c)^2} + \tfrac{bcfhv^*}{(s^*+c)^2}. \end{aligned} \tag{2.3.4}$$

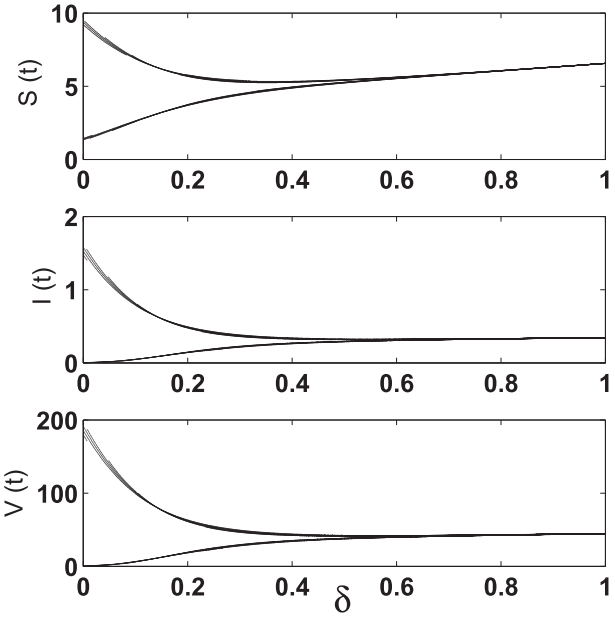

Figure 5: Equilibrium solutions of S, I and V are plotted as a function of recovery rate $\delta \leq 1.0$

From Routh-Hurwitz criterion, E^* is locally asymptotically stable if and only if $A_2 > 0, A_0 > 0$ and $A_2A_1 - A_0 > 0$.

From the signs of those defined in (2.3.4), it is clear that $A_2 > 0$. It is easy to verify that $A_0 > 0$ for all parametric values, provided

$$(i)\ \ max(\tfrac{g}{a}, s^*) < f, \quad (ii)\ \ i^* > \tfrac{1+g}{1+a}. \tag{2.3.5}$$

It is also easy to verify that, $A_2A_1 - A_0 > 0$ for all parametric values provided,

(i) $max(\frac{m+f}{2}, \frac{m+f}{a}) < s^* < min(\frac{f}{a(1+a)}, \frac{f^2}{m+f+g}, 2g)$,
(ii) $max(3as^*, 2g, \frac{g^2}{v^*}, \frac{a^2}{4}, \frac{g(1+a)}{a^2}, \frac{abs^*}{v^*}) < f < \frac{g^2}{2(1+g)}$,
(iii) $min(\frac{2f}{g+f}, \frac{f}{f+g}) > a$,
(iv) $m > max(\frac{g}{s^*}, \frac{2f+1}{g}, 2(1+g))$,
(v) $c > \frac{m+f}{s^*}$. (2.3.6)

From (2.3.5) and (2.3.6) it is obvious that system (2.7) is always for all parametric values and hence completes the theorem.

2.4 Global stability of the system

The Equilibrium $E^*(s^*, i^*, v^*)$ is local asymptotic stable, we construct the Lyapunov function

$$\begin{aligned} U(s,i,v) &= w_1(s - s^* - s^* \ln \tfrac{s}{s^*}) + w_2(i - i^* - i^* \ln \tfrac{i}{i^*}) \\ &\quad + w_3(v - v^* - v^* \ln \tfrac{v}{v^*}). \end{aligned}$$

Calculate the upper right derivation $U(s^*, i^*, v^*)$ along

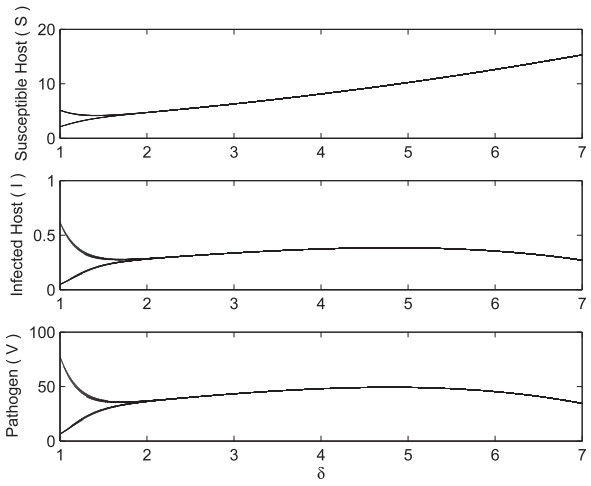

Figure 6: Equilibrium solutions of S, I and V are plotted as a function of recovery rate $\delta \geq 1.0$

the system(2.7) we obtain,

$$D^+U(s^*,i^*,v^*) = w_1\frac{s-s^*}{s}\frac{ds}{dt} + w_2\frac{i-i^*}{i}\frac{di}{dt} + w_3\frac{v-v^*}{v}\frac{dv}{dt}$$
$$= -w_1(s-s^*)^2 - bw_1(s-s^*)(\frac{v}{s+c} - \frac{v^*}{s^*+c}) - (w_1 + aw_1 - aw_2)(s-s^*)(i-i^*) - mw_1(s-s^*)(\frac{i}{s} - \frac{i^*}{s^*}) + w_1(s-s^*)(\frac{i}{s} - \frac{i^*}{s^*}) + bw_2(i-i^*)(\frac{sv}{i(s+c)} - \frac{s^*v^*}{i^*(s^*+c)}) + gw_3(v-v^*)(\frac{i}{v} - \frac{i^*}{v^*}) - bw_3(v-v^*)(\frac{s}{s+c} - \frac{s^*}{s^*+c}) < 0. \quad (2.4.1)$$

When, $w_1 \geq w_2$ and $s \in (0,\infty)$, $i \in (0,\infty)$ and $v \in (0,\infty)$, then the minimum and maximum of$\frac{sv}{i(c+s)}$, $\frac{i}{s}$ and $\frac{i}{v}$ are tends to zero respectively.
Thus, $D^+U(s^*,i^*,v^*) \leq 0$, According to the Lyapunov-LaSalle inveriance principal, $E^*(s^*,i^*,v^*)$ is globally asymptotically stable.

2.5 Numerical solutions of the model Equations

Theoretical analysis of the model is done to explore stability, equilibria and uniqueness of the solutions and their boundedness and global stability of the system. But, for physical realization of the time evolution of different host and pathogen populations with varying model parameters, we consider numerical solutions of the set of equations (2.6). This enables us to visualize the dynamical behaviors of variables S, I, and V. Values of different constant model parameters, as given in Table.1, were chosen from the amassed literature in the field. Note that we want to emphasize the role of the recovery rate within the model.

With the positive octant restriction on S, I, V at $t = 0$ (i.e., $S > 0$, $I > 0$, $V > 0$) we have chosen $S(0) = 2$, $I(0) = 1.5$, $V(0) = 11$. We have considered variation in the recovery rate (δ). It is to be mentioned here that δ is taken in arbitrary units. To begin with, we check the time evolution of S, I, and V with increasing δ.

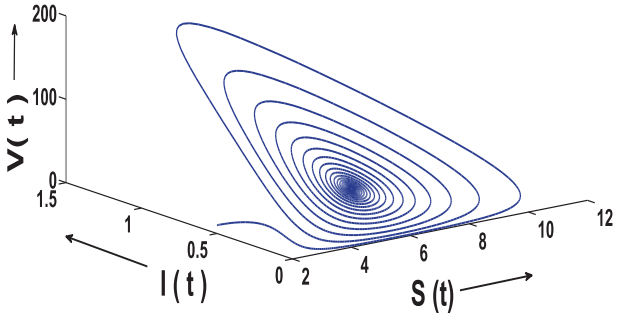

Figure 7: Phase Plane Population densities of Susceptible host (S), Infected host(I) and Pathogen (V) are plotted as a function of time for the Recovery rate $\delta = 0.6$. Other parameters are as in Table.1.

Table.1. Values of parameters used for models dynamics calculations.

Parameter	Definition	Default Value (day $^{-1}$)
r	Maximal growth rate of susceptible host	0.2
K	Carrying capacity	20 unit designated area
h_γ	Half-maximal at a target cell density	9 unit designated area
λ	Force of infection through contact with infected host	0.2 unit designated area
γ	Force of infection through contact with pathogens	0.04 unit designated area
d	Lysis death rate of infected host	2.5 liter
η	Pathogens replication factor	115
μ	Mortality rate of pathogen	2.2

In Figure 2, we have shown these hosts and pathogen populations as a function of time for $\delta = 0.2$. Note that, we have gone upto a time $t = 350$ days. This is because, a thorough check on the system reveals stabilization of all these populations well before $t = 350$ and within this the characteristic features of the system are manifested. In Figure 2, we find oscillatory solutions for all three populations bounded by stable upper and lower limits. As we increase δ, the upper and lower limits of solutions come closer (see Figure3). Beyond some δ the two limits of solutions merge into one and thereafter, unique stable solutions for all three populations exist (see Figure 4).

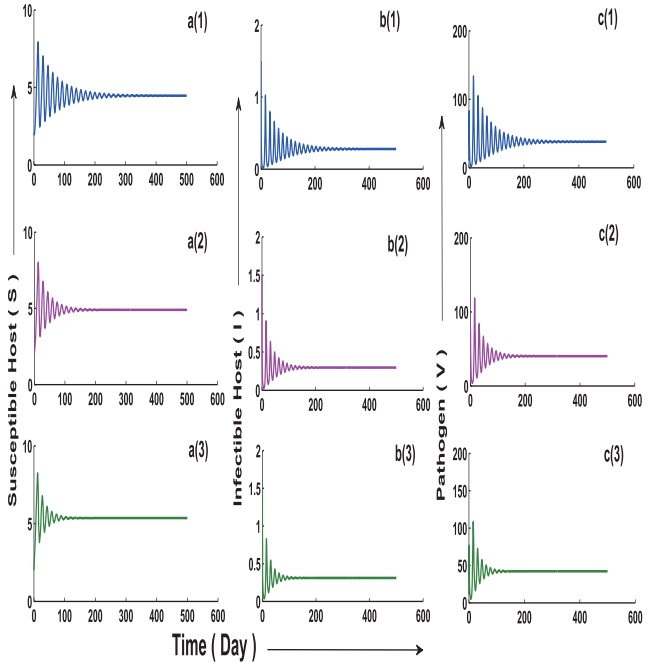

Figure 8: Population densities of Susceptible host (S), Infected host (I) and Pathogen (V) are plotted as a function of time for the Recovery rate $\delta = 0.2, 0.4, 0.6$ and $\tau = 1$. Other parameters are as in Table.1.

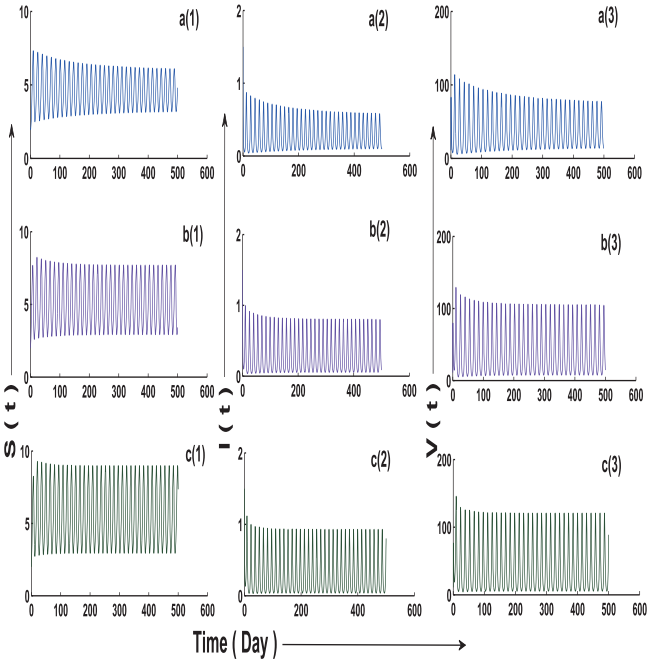

Figure 9: Population densities of Susceptible host (S), Infected host (I) and Pathogen (V) are plotted as a function of time for the Recovery rate $\delta = 0.2, 0.4, 0.6$ and $\tau = 9$. Other parameters are as in Table.1.

In Figure 5(a), Figure 5(b), and Figure 5(c) we have plotted stable solutions for S,I, and V populations for small values of $0 < \delta \leq 1$. Here we find that with $\delta \leq 0.6$ stable solutions are oscillatory for all three populations where bifurcating line towards lower $\delta \sim 0.6$ denote the stable single solution of each population.

Figures 6 contains stable and unique solutions for different populations for larger ($\delta \geq 1$). We find that stable (solution) value of susceptible host increases monotonically, but the same for infected host rises faster and similar rise in pathogen stable solution is the steepest. With $\delta \leq 1$, the system will be stable for small time span but, for $\delta \geq 1$ the system undergoes initially bifurcated and there after the susceptible host populations increases monotonically, and other two populations that is infected hosts and pathogens are goes to extinction.

The phase plane S- I- V (Figure 7) represents the trajectory starting with the initial point which exhibits the limit cycle oscillation and after some time it moves towards the interior equilibrium point.

3 Time delayed model

In this section we have introduced a time delay in the recovery term of our basic mathematical model (2.6) of the host-pathogen interactions in lieu of this recovery from pathogenic infection which move to add to the susceptible host population. We are considering that this recovery would stem out from immunization or vaccination. In that sense it is obvious that there exists a finite time lag or delay in the process of recovery and this finite time lag exist between actively infected host and getting its subsequent recovery. Such realistic time lag has been incorporated in the model under consideration. Thus equations (2.6) can be written as:

$$\begin{aligned} \frac{dS}{dt} &= rS(1 - \frac{S+I}{K}) - \lambda SI - \frac{\gamma SV}{h_\gamma + S} + \delta I(t-\tau) \\ \frac{dI}{dt} &= \lambda SI + \frac{\gamma SV}{h_\gamma + S} - dI - \delta I \\ \frac{dV}{dt} &= -\frac{\gamma SV}{h_\gamma + S} + \eta dI - \mu V. \end{aligned} \tag{3.1}$$

The variables of model equations (3.1) are to be made dimensionless for the sake of simplicity. Thus the rescaled equations are,

$$\begin{aligned} \frac{ds}{dt} &= s(1 - (s+i)) - asi - \frac{bsv}{c+s} + mi(t-\tau) \\ \frac{di}{dt} &= asi + \frac{bsv}{c+s} - fi - mi \\ \frac{dv}{dt} &= -\frac{bsv}{c+s} + gi - hv \end{aligned} \tag{3.2}$$

where, $a = \frac{\lambda K}{r}$, $b = \frac{\gamma K^2}{r}$, $c = \frac{h_\gamma}{r}$, $m = \frac{\delta}{r}$, $f = \frac{d}{r}$, $g = \frac{\eta d}{r}$, and $h = \frac{\mu}{r}$.

Equation (3.2) has only one positive root, existence and uniqueness of the steady state is confirmed by Descartses

rule of sing. Now we investigate the stability of the steady state $E^*(s^*, i^*, v^*)$ by linearization $s = s' - s^*$, $i = I' - i^*$, $v = v' - v^*$. Then we obtain the characteristic equation of the system (3.2) is given by

$$\theta^3 + A\theta^2 + (B + Ce^{-\theta\tau})\theta + D + Ee^{-\theta\tau} = 0. \quad (3.3)$$

Where,

$$\begin{aligned}
A &= (2-a)s^* - 1 + (a+1)i^* + (m+f+h) + \tfrac{bs^*}{s^*+c} \\
&\quad + \tfrac{bcv^*}{(s^*+c)^2} (> 0), \\
B &= fh - f - h + fi^* + afi^* + hi^* + ahi^* - m + hm \\
&\quad + mi^* + ami^* + as^* + 2fs^* + 2hs^* - ahs^* + 2ms^* \\
&\quad - \tfrac{bs^*}{s^*+c} + \tfrac{bgs^*}{s^*+c} + \tfrac{bs^*i^*}{s^*+c} + \tfrac{abs^*i^*}{s^*+c} + \tfrac{bms^*}{s^*+c} + \tfrac{2b(s^*)^2}{s^*+c} \\
&\quad + \tfrac{bfs^*}{s^*+c} - \tfrac{ab(s^*)^2}{s^*+c} + \tfrac{bcfv^*}{(s^*+c)^2} + \tfrac{bcmv^*}{(s^*+c)^2} + \tfrac{bcs^*v^*}{(s^*+c)^2} (> 0), \\
C &= ami^* \ (> 0), \\
D &= fhi^* - fh + afhi^* - hm + hmi^* + ahmi^* + ahs^* \\
&\quad + 2fhs^* + 2hms^* - 2ah(s^*)^2 - \tfrac{bfs^*}{c+s^*} - \tfrac{bgs^*}{c+s^*} + \tfrac{bfs^*i^*}{s^*+c} \\
&\quad + \tfrac{abfs^*i^*}{s^*+c} + \tfrac{bgs^*i}{s^*+c} - \tfrac{bms^*}{s^*+c} + \tfrac{bms^*i^*}{s^*+c} + \tfrac{abms^*i^*}{s^*+c} + \tfrac{ab(s^*)^2}{s^*+c} \\
&\quad + \tfrac{2bf(s^*)^2}{s^*+c} + \tfrac{2bg(s^*)^2}{s^*+c} - \tfrac{2ab(s^*)^3}{s^*+c} + \tfrac{2b^2cg(s^*)^2v^*}{(s^*+c)^3} \\
&\quad + \tfrac{2bm(s^*)^2}{s^*+c} + \tfrac{2b^2c(s^*)^2v^*}{(s^*+c)^3} + \tfrac{2ab^2c(s^*)^2v}{(s^*+c)^3} \\
&\quad + \tfrac{2abgs^*i^*}{s^*+c} + \tfrac{bcfhv^*}{(s^*+c)^2} + \tfrac{bchmv^*}{(s^*+c)^2} + \tfrac{bchs^*v^*}{(s^*+c)^2} (> 0) \\
E &= ahmi^* - \tfrac{abms^*i^*}{s^*+c} - \tfrac{2b^2cms^*v^*}{(s^*+c)^3} - \tfrac{bchmv^*}{(s^*+c)^2} \ (> 0).
\end{aligned} \quad (3.4)$$

Now to determine the nature of the stability, we require the sign of the real parts of the roots of the system(3.3)

$$\Phi(\theta, \tau) = \theta^3 + A\theta^2 + (B + Ce^{-\theta\tau})\theta + D + Ee^{-\theta\tau}. \quad (3.5)$$

Substituting $\theta = u_1(\tau) + i\omega(\tau)$ in (3.3) and separating real and imaginary parts we obtain the following transcendental equations:

$$\begin{aligned}
&u_1^3 - 3u_1\omega^2 + A(u_1^2 - \omega^2) + Bu_1 + cu_1e^{-u_1\tau}\cos\omega\tau \\
&+c\omega e^{-u_1\tau}\sin\omega\tau + D + Ee^{-u_1\tau}\cos\omega\tau = 0
\end{aligned} \quad (3.6)$$

$$\begin{aligned}
&3u_1^2\omega - \omega^3 + 2Au_1\omega + + B\omega + C\omega e^{-u_1\tau}\cos\omega\tau \\
&-Cu_1e^{-u_1\tau}\sin\omega\tau - Ee^{-u_1\tau}\sin\omega\tau = 0.
\end{aligned} \quad (3.7)$$

3.1 Sufficient Conditions for Nonexistence of Delay Induced Instability:

To find the conditions for nonexistence of delay induced instability, we now use the following theorem of [33].

Theorem 3.1.1: A set of necessary and sufficient conditions for the equilibrium E^* to be asymptotically stable for all $\tau \geq 0$ is the following:
(i)Real parts of all the roots of $\phi(\theta, 0) = 0$ are negative.
(ii) For real ω and $\tau \geq 0$, $\phi(i\omega, \tau) \neq 0$, where $i = \sqrt{-1}$.

Proof: Here $\phi(\theta, 0) = 0$ has roots whose real parts are negative provided (3.5) holds. Now for $\omega = 0$,

$$\Phi(0, \tau) = D + E \neq 0. \quad (3.1.1)$$

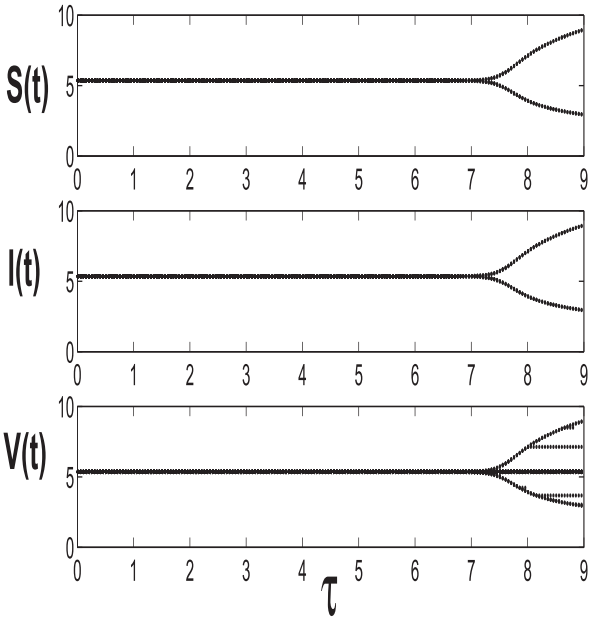

Figure 10: Population densities of Susceptible host (S), Infected host (I) and Pathogen (V) are plotted as a function of τ.

For $\omega \neq 0$,

$$\begin{aligned}
&\phi(i\omega, \tau) = -i\omega^3 - A\omega^2 + (B + Ce^{-i\omega\tau})i\omega \\
&+(D + Ee^{-i\omega\tau})
\end{aligned} \quad (3.1.2)$$

Separating real and imaginary parts we get,

$$A\omega^2 - D = C\omega\sin\omega\tau + E\cos\omega\tau \quad (3.1.3)$$

and

$$\omega^3 - B\omega = C\omega\cos\omega\tau - E\sin\omega\tau \quad (3.1.4)$$

squaring and adding the above two equation, we get

$$(A\omega^2 - D)^2 + (\omega^3 - B\omega)^2 = C^2\omega^2 + E^2. \quad (3.1.5)$$

Let the right hand side of (3.1.5) be denoted by $f(\omega)$.

Now for arbitrary real ω , we get from(3.1.5)

$$f(\omega) \leq a^2\omega^4 + (c^2 - 2aE)\omega^2 + E^2. \quad (3.1.6)$$

Therefore a sufficient condition for the non existence of a real number ω satisfying $\phi(i\omega, \tau) = 0$ can now be obtained from (3.1.5) and (3.1.6) as

$$\begin{aligned}
&\omega^6 + (A^2 - 2B)\omega^4 + (B^2 - 2AD - C^2)\omega^2 \\
&+D^2 - E^2 \geq 0.
\end{aligned} \quad (3.1.7)$$

The inequality which we can write in the form of

$$\omega^6 + P\omega^4 + Q\omega^2 + R_1 > 0 \quad (3.1.8)$$

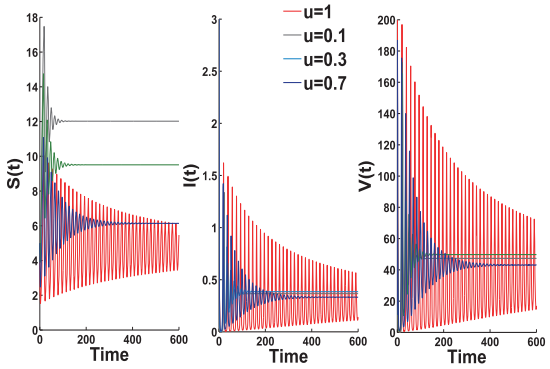

Figure 11: Population of S, I, V for the cases without control and with control.

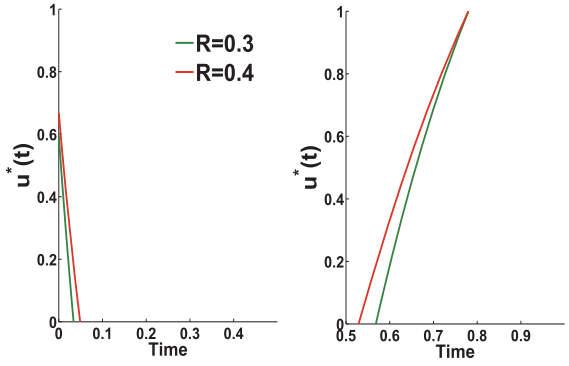

Figure 12: Optimal treatment schedule with different weight factor R.

where,

$$P = A^2 - 2B, \quad Q = B^2 - 2AD - C^2, \\ R_1 = D^2 - E^2. \tag{3.1.9}$$

The sufficient conditions can be obtained if,

$$(i) \quad g > max(\tfrac{2a(s^*)^2v^*}{m+f}, \tfrac{mv^*}{i^*}, \tfrac{m+f}{2}), \\ (ii) \; m < min(a+1, s^*(a+1)), \\ (iii) \quad i^* > max(\tfrac{s^*(s^*+c)}{2c}, \tfrac{1}{a+1}, \tfrac{2(1+m+f)}{(a+1)}), \\ (iv) \quad s^* > \tfrac{m+f}{2m+2f+a}, \\ (v) \quad m+f > max(1, a+1, as^*, \tfrac{as^*}{g}, \tfrac{s^*(as^*+ac+b)}{s^*+c}). \tag{3.1.10}$$

Therefore condition (i) and (ii) of the above theorems are satisfied if (3.1.5) holds.

3.2 Criterion for Preservation of Stability, Instability and Bifurcation Results:

Let us consider θ and hence u_1 and ω as functions of τ. We are interested in the change of stability of E^* which will occur at the values of τ for which $u_1 = 0$ and $\omega \neq 0$. Let $\hat{\tau}$ be such that for which $u_1(\hat{\tau}) = 0$ and $\omega(\hat{\tau}) = \hat{\omega} \neq 0$. Then equations (3.6) and (3.7) become

$$-A\hat{\omega}^2 + C\hat{\omega}\sin\hat{b}\hat{\tau} + D + E\cos\hat{\omega}\hat{\tau} = 0, \tag{3.2.1}$$

$$-\hat{\omega}^3 + B\hat{\omega} + C\hat{\omega}\cos\hat{\omega}\hat{\tau} - E\sin\hat{\omega}\hat{\tau} = 0. \tag{3.2.2}$$

Now eliminating $\hat{\tau}$ we get

$$\hat{\omega}^6 + (A^2 - 2B)\hat{\omega}^4 + (B^2 - C^2 - 2AD)\hat{\omega}^2 \\ + D^2 - E^2 = 0. \tag{3.2.3}$$

To analyze the change in the behavior of the stability of E^* with respect to τ, we examine the sign of $\frac{du_1}{d\tau}$ as u_1 crosses zero. If this derivative is positive (negative) then clearly a stabilization (destabilization) can not take place at that value of $\hat{\tau}$. We differentiate equations (3.6) and (3.7) w.r.t. τ, then setting $\tau = \hat{\tau}$, $u_1 = 0$ and $\omega = \hat{\omega}$ we get,

$$X\tfrac{du_1}{d\tau}(\hat{\tau}) + Y\tfrac{d\omega}{d\tau}(\hat{\tau}) = \alpha \\ -Y\tfrac{du_1}{d\tau}(\hat{\tau}) + X\tfrac{d\omega}{d\tau}(\hat{\tau}) = \beta. \tag{3.2.4}$$

Where,

$$X = -3\hat{\omega}^2 + B - C\cos\hat{\omega}\hat{\tau} - \hat{\tau}[E\cos\hat{\omega}\hat{\tau} + C\hat{\omega}\sin\hat{\omega}\hat{\tau}] \\ Y = -2A\hat{\omega} + C\sin\hat{\omega}\hat{\tau} + \hat{\tau}[C\hat{\omega}\cos\hat{\omega}\hat{\tau} - E\sin\hat{\omega}\hat{\tau}] \\ \alpha = E\hat{\omega}\sin\hat{\omega}\hat{\tau} - C\hat{\omega}^2\cos\hat{\omega}\hat{\tau} \\ \beta = E\hat{\omega}\cos\hat{\omega}\hat{\tau} + C\hat{\omega}^2\sin\hat{\omega}\hat{\tau}. \tag{3.2.5}$$

Solving (3.2.4) we can write,

$$\tfrac{du_1}{d\tau}(\hat{\tau}) = \tfrac{\alpha X - \beta Y}{X^2+Y^2}. \tag{3.2.6}$$

$\frac{du_1}{d\tau}(\hat{\tau})$ has the same sign as $\alpha X - \beta Y$. From (3.2.5) after simplification and solving (3.2.1) and (3.2.2) again we get,

$$\alpha X - \beta Y = \hat{\omega}^2[3\hat{\omega}^4 + 2(A^2 - 2B)\hat{\omega}^2 \\ + (B^2 - C^2 - 2AD)]. \tag{3.2.7}$$

$$\text{Let} \quad F(z) = z^3 + P_1 z^2 + P_2 z + P_3,$$

where,

$$P_1 = A^2 - 2B, \quad P_2 = B^2 - C^2 - 2AD, \\ \text{and} \quad P_3 = D^2 - E^2 \tag{3.2.8}$$

which is the left hand side of the equation (3.2.3) with $\hat{\omega}^2 = z$.

$$\text{Therefore,} \quad F(\hat{\omega}^2) = 0. \tag{3.2.9}$$

$$\text{Now,} \quad \tfrac{dF}{dz}(\hat{\omega}^2) = 3\hat{\omega}^4 + 2P_1\hat{\omega}^2 + P_2 = \tfrac{\alpha X - \beta Y}{\hat{\omega}^2} \\ \Rightarrow \tfrac{dF}{dz}(\hat{\omega}^2) = \tfrac{X^2+Y^2}{\hat{\omega}^2}.\tfrac{du_1}{d\tau}(\hat{\tau}) \\ \Rightarrow \tfrac{du_1}{d\tau}(\hat{\tau}) = \tfrac{\hat{\omega}^2}{X^2+Y^2}.\tfrac{dF}{dz}(\hat{\omega}^2). \tag{3.2.10}$$

Hence the criterion of instability (stability) of E^* are (1) if the polynomial $F(z)$ has no positive root (being contradiction to the existence of $\hat{\omega} > 0$ be real) there can

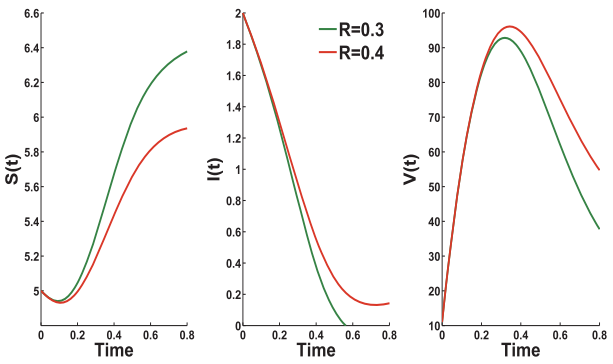

Figure 13: The system behavior for optimal treatment when final time $t_{final} = 1$. Keeping all other parameter as in Table.1.

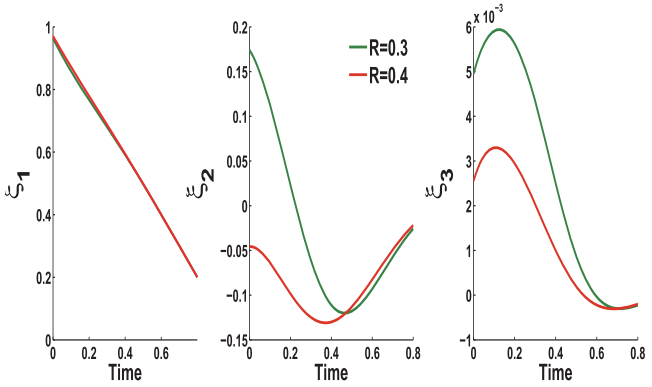

Figure 14: The adjoint variable $\xi_1(t)$, $\xi_2(t)$, $\xi_3(t)$ of the optimality system.

be no change of stability. (2) if $F(z)$ is increasing (decreasing) at all of its positive roots, instability (stability) is preserved. Now in this case, if (I) $P_3 < 0$, $F(z)$ has unique positive real root and then it must increase at that point [since $F(z)$ is a cubic in z, $Lt_{z\to\infty} F(z) = \infty$]. (II) $P_3 > 0$, then (1) is satisfied, i.e. there can be no change of stability. (III)If $P_2 < 0$, $P_3 > 0$ then minimum of $F(z)$ will exist at

$$z_m = \frac{-P_1 + \sqrt{P_1^2 - 3P_2}}{3} \tag{3.2.11}$$

$$\text{and if,} \quad F(Z_m) > 0. \tag{3.2.12}$$

$$\text{i.e.} \quad 2{P_1}^3 - 9P_1P_2 + 27P_3 > 2({P_1}^2 - 3P_2)^{\frac{3}{2}} \tag{3.2.13}$$

$$\text{since,} \quad 27P_3 - 3P_1P_2 > 27P_3.$$

$$\text{Hence} \quad 2P_1(P_1^2 - 3P_2) + 27P_3 - 3P_1P_2 > 27P_3 + 2{P_1}^3. \tag{3.2.14}$$

Thus for equation(3.1.2) to hold it is sufficient that

$$27P_3 - 2{P_1}^3 > 2({P_1}^2 - 3P_2)^{\frac{3}{2}}$$

$$P_2 > \frac{{P_1}^2 - (\frac{27P_3 + 2{P_1}^3}{2})^{\frac{2}{3}}}{3}. \tag{3.2.15}$$

Therefore, we get the following theorem.

Theorem 3.2.1: *If $P_3 < 0$ and if E^* is unstable for $\tau = 0$, it will remain unstable for $\tau > 0$.*

Theorem 3.2.2: *If $P_3 < 0$ and if E^* is asymptotically stable for $\tau = 0$, it is impossible that it remains stable for $\tau > 0$. Hence there exists a $\hat{\tau} > 0$, such that for $\tau < \hat{\tau}$, E^* is asymptotically stable and for $\tau > \hat{\tau}$, E^* is unstable and as τ increases together with $\hat{\tau}$, E^* bifurcates into small amplitude periodic solutions of Hopf type (Marsden and McCracken, 1976)* [34]. The existence of unique $\hat{\tau}$ is given by

$$\hat{\tau} = \frac{1}{\hat{\omega}} \arctan[\frac{BE - \alpha C\hat{\omega}}{\alpha E + C\beta\hat{\omega}}] + \frac{n\pi}{\hat{\omega}}, \quad n = 0, 1, 2.... \tag{3.2.16}$$

Our required $\hat{\tau}$ is given by $n = 0$ in (3.2.16) and hence the Hopf bifurcation criteria is satisfied.

3.3 Numerical Experiment of the Delayed Model of Host Pathogen Interactions

Numerical solution of the model equation (3.1) with the the basic model parameters set to their standard values as in Table.1. In figure 1 we study of the delay model numerically and plot the time series solutions of the model variables corresponding to the three population densities, S, I and V sweeping the values of delay factor as well as δ the recovery rate. We find that delay makes the initial oscillation in the solution trajectories to persist for longer of time. However as δ increase the amplitude of oscillation reduce short of time to moves towards it stable region. This is clearly see in different panels in figure $8(a(1), a(2), a(3))$ for $\delta = 0.2$, in Figure $8(b(1), b(2), b(3))$ for $\delta = 0.4$, and in Figure $8(c(1), c(2), c(3))$ for $\delta = 0.6$.

Again we also see that as τ increases, and for consideration of $\delta = 0.2$, with all the other model parameters are chosen to assume their standard values as in Table.1, the amplitude of oscillation for all three population S, I and V bounded by upper and lower limits. As increases $\delta = 0.4$, $\delta = 0.6$ the upper and lower limits of solution come enlarge. This is clearly see in different panels in Figure $9(a(1), b(1), c(1))$ for $\delta = 0.2$, in Figure $9(a(2), b(2), c(2))$ for $\delta = 0.4$ and in Figure $9(a(3), b(3), c(3))$ for $\delta = 0.6$.

Thus from Figure 8 and from Figure 9, it is clear that an increasing τ makes the oscillations to be carried further on the time scale. This is a signature of local instability inflicted by the delay in the recovery. However an increase in the numerical value of parameter δ, the amplitude of oscillations in the solutions and reduces the time span of the persistence of oscillations. This is clearly demonstrated by the plots of different panels in Figure 8. This plots seems to signified that there is a competition between the delay factor τ and the recovery rate of infected pathogens δ for dominance within the system.

However in Figure 9 specially we observe that for small values of τ, when inflicted with considering $\delta = 0.2$ initial value of recovery rate of infected host, local instability is not so high. But increasing value of δ the asymptotic time series solutions are oscillatory but stable and bounded by an upper and a lower limits. As δ increases further the boundary between the upper and lower limits of oscillations enlarges monotonically.

For the above set of parameters(Table.1) we can evaluate the value of $\tau_0 = 7.11$. In figure 10 the system undergoes a Hopf-bifurcation at the interior equilibrium point $E^*(5.38, 5.38, 5.35)$ when $\tau = \tau_0$. We observe that when $\tau < \tau_0$ the system is stable and when the value of τ crosses the critical value τ_0 the system switches a unstable condition from the stable condition.

4 Optimal control strategy of host-pathogen interactions

In this section we have used an optimal control theory strategy to host-pathogen interactions model with therapeutic point of view and such view in reality as a way to suppress the pathogenic production. Also it is to examine whether any qualitative differences in treatment outcomes among the models have a significant impact on the optimal therapeutic value. Thus on that stare, an optimal therapeutic treatment is considered with the control affecting interaction term $\frac{bsv}{c+s}$. This control represents the percentage of effect of the therapy that reflects an interaction of host with the pathogens and this interaction specially implies that the pathogens are maximally infect γ susceptible hosts per day. This infection rate is half maximal at susceptible host population density of h_γ host. Thus in equation (2.6) the control $u(t)$ multiplies the parameter γ in first two equation. Here our main object is to minimize the infected host population as well as minimize the systemic cost of drug treatment. In order to that we formulate an optimal control problem. We also want to maximize the level of susceptible host. So in the model (2.6) we use a control variable $u(t)$, represents the drug dose satisfying $0 \le u(t) \le 1$. Here $u(t) = 1$ represents the maximal use of therapy and $u(t) = 0$ represents no treatment.

We choose our control class measurable function defined on $[t_{start}, t_{final}]$ with the condition $0 \le u(t) \le 1$, i.e $U := \{u(t)|u(t)$ is measurable, $0 \le u(t) \le 1$, $t \in [t_{start}, t_{final}]\}$. Based on the above assumption, the optimal control problem is formulated as:

$$\begin{aligned}
\tfrac{dS}{dt} &= rS(1-\tfrac{S+I}{K}) - \lambda SI - u(t)\tfrac{\gamma SV}{h_\gamma+S} + \delta I \\
\tfrac{dI}{dt} &= \lambda SI + u(t)\tfrac{\gamma SV}{h_\gamma+S} - dI - \delta I \\
\tfrac{dV}{dt} &= -\tfrac{\gamma SV}{h_\gamma+S} + \eta dI - \mu V
\end{aligned} \tag{4.1}$$

Define the objective function

$$J(u) = \int_{t_{start}}^{t_{final}} [S(t) - R\tfrac{1}{2}(1-u(t))^2]dt \tag{4.2}$$

If the control $u(t) = 0$ corresponds to maximal use of drug,then the maximal cost is representedas $(1 - u(t))$.The parameter $R \ge 0$ represents the desired 'weight' on the benefit and cost. The goal,therefore is to characterize the optimal control u^* satisfying $max_{0\le u\le 1} J(u) = J(u^*)$.
Define the Lagrangian to be:

$$\begin{aligned}
&L(S, I, V, u, \xi_1, \xi_2, \xi_3) = S(t) - R\tfrac{1}{2}(1-u(t))^2 \\
&+\xi_1(rS(1-\tfrac{S+I}{K}) - \lambda SI - u(t)\tfrac{\gamma SV}{h_\gamma+S} + \delta I) \\
&+\xi_2(\lambda SI + u(t)\tfrac{\gamma SV}{h_\gamma+S} - dI - \delta I) \\
&+\xi_3(-\tfrac{\gamma SV}{h_\gamma+S} + \eta dI - \mu V) + \omega_1(t)u(t) + \omega_2(t)(1-u(t))
\end{aligned} \tag{4.3}$$

$\omega_1(t) \ge 0, \omega_2(t) \ge 0$ are the penalty multipliers satisfying $\omega_1(t)u(t) = 0$ and$\omega_2(t)(1-u(t)) = 0$. Thus, the Maximum Principal give the existence of adjoint variables satisfying:

$$\begin{aligned}
\xi_1' &= -\tfrac{\partial L}{\partial S} = -[(1 + \xi_1 r(1-\tfrac{2S+I}{K}) - \lambda I - u(t)\tfrac{\gamma V}{h_\gamma+S} \\
&\quad + u(t)\tfrac{\gamma SV}{(h_\gamma+S)^2}) + \xi_2(\lambda I + u(t)\tfrac{\gamma V}{h_\gamma+S} - u(t)\tfrac{\gamma SV}{(h_\gamma+S)^2}) \\
&\quad + \xi_3(-\tfrac{\gamma V}{h_\gamma+S} + \tfrac{\gamma SV}{(h_\gamma+S)^2})] \\
\xi_2' &= -\tfrac{\partial L}{\partial I} = -[(\xi_1\tfrac{rS}{K} - \lambda S + \delta) \\
&\quad + \xi_2(\lambda S - d - \delta) + \xi_3\eta] \\
\xi_3' &= -\tfrac{\partial L}{\partial V} = -[\xi_1(-u(t)\tfrac{\gamma S}{h_\gamma+S}) + \xi_2 u(t)(\tfrac{\gamma S}{h_\gamma+S}) \\
&\quad + \xi_3(-\tfrac{\gamma S}{h_\gamma+S} - \mu)].
\end{aligned} \tag{4.4}$$

Where $\xi_i(t_{final}) = 0$ for i=1,2,3 are the transversality condition. The Lagrangian is maximized with respect to the with respect to u at the optimal u^*,so the derivative of the Lagrangian with respect to u at u^* is zero. Since,

$$\begin{aligned}
L &= -\xi_1 u(t)\tfrac{\gamma SV}{h_\gamma+S} + \xi_2 u(t)\tfrac{\gamma SV}{h_\gamma+S} + \omega_1(t)u(t) \\
&\quad + \omega_2(t)(1-u(t)) - R\tfrac{1}{2}(1-u(t))^2 + \\
&\quad + \text{terms without u(t).}
\end{aligned} \tag{4.5}$$

Differentiating this expression for L with respect to u gives:

$$\begin{aligned}
\tfrac{\partial L}{\partial u} &= (\xi_2 - \xi_1)\tfrac{\gamma SV}{h_\gamma+S} + \omega_1(t) - \omega_2(t) \\
&\quad + R(1-u(t)) = 0 \quad \text{at} \quad u^*.
\end{aligned} \tag{4.6}$$

Solving for the optimal control yields

$$u^*(t) = \tfrac{(\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S} + \omega_1(t) - \omega_2(t) + R}{R}. \tag{4.7}$$

Now we are try to find out $u^*(t)$, using different penalty multipliers in three different cases:

(i) For $t|0 \le u^*(t) \le 1$, we have $\omega_1(t) = \omega_2(t) = 0$, hence the optimal control is;

$$u^*(t) = \tfrac{(\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S} + R}{R}$$

(ii) For $t|u^*(t) = 1$, we have $\omega_1 = 0$
Hence, $u^*(t) = 1 = \frac{(\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S}}{R} + 1$,
which implies

$$0 \leq \omega_2(t) = (\xi_2 - \xi_1)\frac{\gamma SV}{h_\gamma+S}, \quad 1 \leq \frac{(\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S}+R}{R}.$$

(iii) For $t|u^*(t) = 0$, we have $\omega_1(t) \geq 0, \omega_2(t) = 0$, hence the optimal control is;

$$u^*(t) = 0 = \frac{(\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S}+\omega_1(t)+R}{R}.$$

Therefore, $\omega_1(t) \geq 0$ implies that, $\frac{(\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S}+R}{R} \leq 0$, hence

$$(\frac{(\xi_2-\xi_1)\gamma SV+R(h_\gamma+S)}{R(h_\gamma+S)})^+ = 0 = u^*(t).$$

Combining the above three cases, the optimal control is characterized as

$$u^*(t) = \min((\frac{(\xi_2-\xi_1)\gamma SV+R(h_\gamma+S)}{R(h_\gamma+S)})^+, 1). \tag{4.8}$$

Where,

$$(\frac{(\xi_2-\xi_1)\gamma SV+R(h_\gamma+S)}{R(h_\gamma+S)})^+ = \begin{bmatrix} \frac{(\xi_2-\xi_1)\gamma SV}{R(h_\gamma+S)}+1, & if \quad (\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S}+R>0 \\ 0, & if \quad (\xi_2-\xi_1)\frac{\gamma SV}{h_\gamma+S}+R\leq 0 \end{bmatrix}.$$

If $(\xi_2 - \xi_1) < 0$ for some t,then $u^*(t) \neq 1$.hence.$0 < u^*(t) < 1$ for those t,which Infected host should be administered.

Theorem 4.1: An optimal control u^* for equation (4.1) which maximizes the objective function (4.2) is characterized by (4.8), where the notation $\varepsilon^+ = \max(\varepsilon, 0)$.

The uniqueness of solutions to the optimal system equation (4.1), completed with (4.4) together with u^* characterization equation (4.8), can be obtained by the standard results. Thus the unique optimal control is represented in term of the unique solution of the optimal system. Note that we could have only treated the case $\epsilon \leq u \leq 1, \epsilon > 0$, which would say that the drug never completely stopped infected host reproduction.

4.1 Existence of an Optimal Control

The boundebness of solutions of the system (4.1) for the finite time interval is used to prove the existence of an optimal system are determined.

$$\begin{array}{ll} \frac{d\bar{S}}{dt} = r\bar{S} + \delta\bar{I}, & \bar{S}(t) = \bar{S}_0 \\ \frac{d\bar{I}}{dt} = \lambda\bar{S}\bar{I} + \frac{\gamma\bar{S}\bar{V}}{h_\gamma+S}, & \bar{I}(t) = \bar{I}_0 \\ \frac{d\bar{V}}{dt} = \eta d\bar{I}, & \bar{V}(t) = \bar{V}_0 \end{array}$$

or,

$$\begin{pmatrix} \bar{S} \\ \bar{I} \\ \bar{V} \end{pmatrix}' = \begin{pmatrix} r & \delta & 0 \\ \lambda\bar{I} + \frac{\gamma\bar{V}}{h_\gamma+S} & \lambda\bar{S} & \frac{\gamma\bar{S}}{h_\gamma+S} \\ 0 & \eta d & 0 \end{pmatrix} \begin{pmatrix} \bar{S} \\ \bar{I} \\ \bar{V} \end{pmatrix}.$$

Since this is a linear system in finite time with bounded coefficient, then the suppersolution $\bar{S}$, $\bar{I}$, $\bar{V}$ are uniformly bounded.
Theorem 4.1.1: There exist an optimal control u^* that maximizes the objective function $J(u)$.
To proved this theorem,the following conditions must be satisfied.
(I) The class of all initial conditions with a control u such that u is a Lebesgueintegrable function on $[t_{start}, t_{final}]$ with values in the admissible control set and such that the state system is satisfied is not empty.
(II) The admissible control is closed and convex.
(III) The right hand side of the state system is continuous,is bounded above by a sum of the bounded control and the state,and can be written as a linear function of$u$ with coefficients depending on time and the state variable.
(IV) The integrand of the function is concave on the admissible control set and is bounded above dy $c_2 - c_1|1 - u|^\rho$,where $c_1 > 0$, and $\rho > 1$.
First, existence result in [37] for the state system (4.1) for bounded coefficient is invoked. The control set is closed and convex by defination.The right hand side of the system (4.1) has at most linear growth since the state solution are a Priori bounded.In addition, the integrand in the functional $[S(t) - R\frac{1}{2}(1 - u(t))^2]$, is concave on the admissible control set. To complete the existence of an optimal control, one use that $[S(t) - R\frac{1}{2}(1 - u(t))^2] \leq c_2 - c_1|1 - u|^\rho$, where $c_1 > 0$ and $\rho > 1$. We conclude there exists an optimal control.

4.2 Uniqueness of the Optimal System

Theorem 4.2.1: For t_{final} sufficiently small,bounded solutions to the optimal system are unique.
Proof: Suppose $(S, I, V, \xi_1, \xi_2, \xi_3)$ and $(\bar{S}, \bar{I}, \bar{V}, \bar{\xi_1}, \bar{\xi_2}, \bar{\xi_3})$ are two different solutions of our optimal system (4.1) and (4.8). Let $S = e^{\lambda_1 t}p_1$, $I = e^{\lambda_1 t}p_2$, $V = e^{\lambda_1 t}p_3$, $\xi_1 = e^{-\lambda_1 t}q_1$, $\xi_2 = e^{-\lambda_1 t}q_2$, $\xi_3 = e^{-\lambda_1 t}q_3$ and $\bar{S} = e^{\lambda_1 t}\bar{p_1}$, $\bar{I} = e^{\lambda_1 t}\bar{p_2}$, $\bar{V} = e^{\lambda_1 t}\bar{p_3}$, $\bar{\xi_1} = e^{-\lambda_1 t}\bar{q_1}$, $\bar{\xi_2} = e^{-\lambda_1 t}\bar{q_2}$, $\bar{\xi_3} = e^{-\lambda_1 t}\bar{q_3}$, where $\lambda_1 > 0$.
Therefore, $u = \min((\frac{(q_2-q_1)e^{\lambda_1 t}\gamma p_1 p_3+R(h_\gamma+e^{\lambda_1 t}p_1)}{R(h_\gamma+e^{\lambda_1 t}p_1)})^+, 1)$
and $\bar{u} = \min((\frac{(\bar{q_2}-\bar{q_1})e^{\lambda_1 t}\gamma\overline{p_1 p_3}+R(h_\gamma+e^{\lambda_1 t}\bar{p_1})}{R(h_\gamma+e^{\lambda_1 t}\bar{p_1})})^+, 1)$.

Now we substitute $S = e^{\lambda_1 t}p_1$ in to the first ODE of (4.1) and (4.8) we get,

$$\begin{aligned} \textbf{(1)} \quad & p_1' + \lambda_1 p_1 = rp_1(1 - \tfrac{e^{\lambda_1 t}(p_1+p_2)}{K}) - \lambda_1 e^{\lambda_1 t}p_1 p_2 \\ & - \min((\tfrac{(q_2-q_1)e^{\lambda_1 t}\gamma p_1 p_3+R(h_\gamma+e^{\lambda_1 t}p_1)}{R(h_\gamma+e^{\lambda_1 t}p_1)})^+, 1) \\ & (e^{\lambda_1 t}\tfrac{\gamma p_1 p_3}{h_\gamma+e^{\lambda_1 t}p_1}) + \delta p_2. \end{aligned}$$

Similarly, for $I = e^{\lambda_1 t}p_2$, $V = e^{\lambda_1 t}p_3$, $\xi_1 = e^{-\lambda_1 t}q_1$, $\xi_2 = e^{-\lambda_1 t}q_2$, $\xi_3 = e^{-\lambda_1 t}q_3$ and $\bar{S} = e^{\lambda_1 t}\bar{p_1}$, $\bar{I} = e^{\lambda_1 t}\bar{p_2}$, $\bar{V} = e^{\lambda_1 t}\bar{p_3}$, $\bar{\xi_1} = e^{-\lambda_1 t}\bar{q_1}$, $\bar{\xi_2} = e^{-\lambda_1 t}\bar{q_2}$, $\bar{\xi_3} = e^{-\lambda_1 t}\bar{q_3}$, we obtain

(2). $p_2' + \lambda_1 p_2 = e^{\lambda_1 t}\lambda p_1 p_2$
$+ \min((\frac{(q_2-q_1)e^{\lambda_1 t}\gamma p_1 p_3 + R(h_\gamma + e^{\lambda_1 t}p_1)}{R(h_\gamma+e^{\lambda_1 t}p_1)})^+, 1)e^{\lambda_1 t}\frac{\gamma p_1 p_3}{h_\gamma + e^{\lambda_1 t}p_1}$
$-(d+\delta)p_2,$

(3) $p_3' + \lambda_1 p_3 = -e^{\lambda_1 t}\frac{\gamma p_1 p_3}{h_\gamma + e^{\lambda_1 t}p_1)} + \eta d p_2 - \mu p_3,$

(4) $-q_1' + \lambda_1 q_1 = e^{\lambda_1 t} + q_1[r(1 - e^{\lambda_1 t}\frac{2p_1+p_2}{K}) - e^{\lambda_1 t}\lambda p_2$
$-(\min((\frac{(q_2-q_1)e^{\lambda_1 t}\gamma p_1 p_3 + R(h_\gamma+e^{\lambda_1 t}p_1)}{R(h_\gamma+e^{\lambda_1 t}p_1)})^+, 1))$
$e^{\lambda_1 t}\frac{h_\gamma \gamma p_3}{(h_\gamma+e^{\lambda_1 t}p_1)^2}] + q_2(e^{\lambda_1 t}\lambda p_2 +$
$(\min((\frac{(q_2-q_1)e^{\lambda_1 t}\gamma p_1 p_3 + R(h_\gamma+e^{\lambda_1 t}p_1)}{R(h_\gamma+e^{\lambda_1 t}p_1)})^+, 1))$
$e^{\lambda_1 t}\frac{h_\gamma \gamma p_3}{(h_\gamma+e^{\lambda_1 t}p_1)^2}) - e^{\lambda_1 t}\frac{h_\gamma \gamma p_3 q_3}{(h_\gamma+e^{\lambda_1 t}p_1)^2},$

(5) $-q_2' + \lambda_1 q_2 = (e^{\lambda_1 t}\frac{p_1 q_1 r}{K} - e^{2\lambda_1 t}\lambda p_1 q_1 + \delta q_1 e^{\lambda_1 t}) +$
$q_2(e^{\lambda_1 t}\lambda p_1 - d - \delta) + q_3\eta,$

(6) $-q_3' + \lambda_1 q_3 =$
$(\min((\frac{(q_2-q_1)e^{\lambda_1 t}\gamma p_1 p_3 + R(h_\gamma+e^{\lambda_1 t}p_1)}{R(h_\gamma+e^{\lambda_1 t}p_1)})^+, 1))e^{\lambda_1 t}\frac{\gamma p_1 (q_2-q_1)}{h_\gamma+e^{\lambda_1 t}p_1} -$
$q_3(e^{\lambda_1 t}\frac{\gamma p_1}{h_\gamma+e^{\lambda_1 t}p_1} + \mu).$

Now we subtract the equations for S and $\bar{S}$, I and $\bar{I}$, V and $\bar{V}$, ξ_1 and $\bar{\xi_1}$, ξ_2 and $\bar{\xi_2}$, ξ_3 and $\bar{\xi_3}$. Thereafter multiply each equation by appropriate difference of functions and integrate from t_{start} to t_{final}. Next we add six integral equation and will use estimates to obtain uniqueness. Thus,
$\frac{1}{2}(p_1-\bar{p_1})^2(t_{final}) + \lambda_1\int_{t_{start}}^{t_{final}}(p_1-\bar{p_1})^2 dt$
$\leq r\int_{t_{start}}^{t_{final}}(p_1-\bar{p_1})^2 dt$
$-\frac{r}{K}\int_{t_{start}}^{t_{final}} e^{\lambda_1 t}(p_1^2 - \bar{p_1}^2)(p_1-\bar{p_1})dt$
$-(\frac{r}{K}+\lambda)\int_{t_{start}}^{t_{final}} e^{\lambda_1 t}(p_1 p_2 - \overline{p_1 p_2})(p_1-\bar{p_1})dt$
$-\gamma\int_{t_{start}}^{t_{final}} e^{\lambda_1 t}(u^*\frac{p_1 p_3}{h_\gamma+e^{\lambda_1 t}p_1} - u^*\frac{\overline{p_1 p_3}}{h_\gamma+e^{\lambda_1 t}p_1})(p_1-\bar{p_1})dt$
$+\delta\int_{t_{start}}^{t_{final}}(p_2-\bar{p_2})(p_1-\bar{p_1})dt.$
$\leq C_1\int_{t_{start}}^{t_{final}}[(p_1-\bar{p_1})^2 + (p_2-\bar{p_2})^2 + (p_3-\bar{p_3})^2]dt$
$+ C_2 e^{\lambda_1 t_{final}}\int_{t_{start}}^{t_{final}}[(p_1-\bar{p_1})^2 + (p_2-\bar{p_2})^2 + (q_1-\bar{q_1})^2$
$+ (q_2-\bar{q_2})^2]dt.$

Where the constants $\tilde{C_1}$ and $\tilde{C_2}$ depend on the coefficients and the bounds on states and adjoints. Combining six of these estimates gives

$\frac{1}{2}(p_1-\bar{p_1})^2(t_{final}) + \frac{1}{2}(p_2-\bar{p_2})^2(t_{final})$
$+\frac{1}{2}(p_3-\bar{p_3})^2(t_{final}) + \frac{1}{2}(q_1-\bar{q_1})^2(t_{start})$
$+\frac{1}{2}(q_2-\bar{q_2})^2(t_{start}) + \frac{1}{2}(q_3-\bar{q_3})^2(t_{start})$
$+\lambda_1\int_{t_{start}}^{t_{final}}[(p_1-\bar{p_1})^2 + (p_2-\bar{p_2})^2 + (p_3-\bar{p_3})^2$
$+(q_1-\bar{q_1})^2 + (q_2-\bar{q_2})^2 + (q_3-\bar{q_3})^2]dt$
$\leq (\tilde{C_1} + \tilde{C_2}e^{3\lambda_1 t_{final}})\int_{t_{start}}^{t_{final}}[(p_1-\bar{p_1})^2$
$+(p_2-\bar{p_2})^2 + (p_3-\bar{p_3})^2 + (q_1-\bar{q_1})^2$
$+(q_2-\bar{q_2})^2 + (q_3-\bar{q_3})^2]dt.$

Thus from above equation we conclude that

$(\lambda_1 - \tilde{C_1} - \tilde{C_2}e^{3\lambda_1 t_{final}})\int_{t_{start}}^{t_{final}}[(p_1-\bar{p_1})^2 + (p_2-\bar{p_2})^2$
$+(p_3-\bar{p_3})^2 + (q_1-\bar{q_1})^2 + (q_2-\bar{q_2})^2 + (q_3-\bar{q_3})^2]dt$
$\leq 0.$

where $\tilde{C_1}$, $\tilde{C_2}$ depend on the coefficients and the bounds on p_1, p_2, p_3, q_1, q_2 ,q_3. If we choose λ_1 such that $\lambda_1 > \tilde{C_1} + \tilde{C_2}$ and $t_{final} < \frac{1}{3\lambda_1}\ln(\frac{\lambda_1 - \tilde{C_1}}{\tilde{C_2}})$, then $p_1 = \bar{p_1}$, $p_2 = \bar{p_2}$, $p_3 = \bar{p_3}$, $q_1 = \bar{q_1}$, $q_2 = \bar{q_2}$, $q_3 = \bar{q_3}$.

Thus, we can say that the solution of the system of such nonlinear boundary value problem is unique for a small time interval. The optimal control u^* gives an unique solution of the optimal system. The above optimal control give an optimal treatment strategy for the pathogen infected individual.

4.3 Numerical Experiment of Optimal Control Strategy

For the numerical illustration of the optimal control problem (4.1) and (4.2) we assume $t_{final} = 1$, which can be used as an initial guess. We solve the optimality system by making the changes of the variable $T = t/t_{final}$ and transferring the interval $[0, 1]$. Here T represents the step size which is used for better strategy with a line search method and which will maximize the reduction of performance measure. Here we choose $t_{final} = 1 + \Delta t_{final}$ and initially $t_{final} = 1$. We also assume that $\Delta t_{final} = 0.1$ and our desired value of $t_{final} = 100$. The solution are displayed in Figure 11, Figure 12, Figure 13, Figure 14.

In Figure 11, for non treated system (i.e $u = 1$) the system is unstable, while the system moves to more adequate level when the optimal treatment is used. It has also been observed that the system moves to its stable region more rapidly as u is reduced from 0.7 to 0.1.

In Figure 12, it has been observed that the optimal control $u^*(t)$ reduces with time [for (0,0.5)] and as R reduces for 0.4 to 0.3, $u(t)$ rapidly moves towards its optimal strategy. But for $0.5 < T < 1$ the optimal strategy moves towards no treatment strategy (i.e $u^*(t) = 1$). We also observed that, if the weight factor R is reduced then the optimal treatment is reached to its maximum level. It should be noted here that for lower weight factor this drug is more toxic and during use of this drug it is required in a less amount.

If we consider the time limit of uses of drugs is near about 500 days then what will be the therapeutic effect in our model of host pathogen interactions? It has been shown that from our numerical results that if it is used for less than 10 days the result for best treatment is to be appear for using drug, but if it is introduce for more than 50 days the worst condition will appear inspite of a better one.

From Figure 13 we see that the optimal drug treatment is more effective than the fixed drug treatment. For optimal drug therapy for susceptible host populations increase to its maximal level with short period of time, though it has sharp decline at the end because of cessation of drug enables the infection of rebound to destroy the host population. The infected host population decreases to its

low level but at the end of the treatment schedule, when drug therapy is removed, the infection level eventually rises again. It is also numerically experimented that after using of 'control drug therapy' set in motion, initially pathogen population increases, whereas in a certain period of time for effect of that drug, pathogen population rapidly decreases to its small size population.

5 Discussion and Conclusions

We have considered a mathematical model of a host-pathogen system including a recovery of the infected host to the susceptible. It is also assumed in our model that the spread of disease takes place in two avenues namely, by pathogens as well as by contact of a susceptible host with a infected host and this pathogens are maximally infect γ susceptible hosts per day and this infection rate is half maximal at susceptible host population density of h_γ host. The set of differential equations of the model are solved both analytically and numerically. Here, In the first section we put emphasis on the recovery of the infected host to their healthy class. We have analyzed the model in-depth, particularly to see the effects of host recovery on the model dynamics and its solutions.

In section 1 our theoretical analysis of the existence, uniqueness and boundedness of the asymptotic solutions show that perimetrically conditioned solutions for the model equations do exist and they are unique and bounded in well defined regions of the parameter space. The analysis further show that the system possesses several equilibria, some of which are denoted by $E_0(0,0,0), E_1(1,0,0)$, and $E^*(s^*,i^*,v^*)$. However, by stability analysis of equilibria, we find that the system is unstable around E_0 for all parametric values and E_1 is locally asymptotically stable. Also the system is locally asymptotically stable around E^*. In fact E^* is globally asymptotically stable.

Since infected hosts which do not grow or reproduce but they can recover from pathogenic infection and move to add to the susceptible host population and this recovery would stem out from immunization or vaccination thus there exists a finite time lag or delay in the process of recovery and this finite time lag exist between actively infected host and getting its subsequent recovery. In section 2 we studied "Sufficient Conditions for Nonexistence of Delay Induced Instability" and "Criterion for Preservation of Stability, Instability and Bifurcation Results" to see the dynamics of the proposed model including delay and to explore the crucial system parameters and their ranges in order to obtain different theoretical behaviors predicted from the interaction between susceptible host, infected host and pathogen, and moreover the recovery response against pathogen infected host population through immunization or vaccination.

In section 3 in our research article we have used an optimal control theory paradigm to host-pathogen interactions model with therapeutic outlook and such therapeutic control as a way to suppress the pathogenic production. Our analytical results reveal that how a cost-effective combination of treatment efforts may depend on the population size, cost of implementing treatments control for different parameters of the model.

Complete numerical solutions of the model equations for the parameters as in (Table.1), yield results which are consistent with the parametric conditions obtained analytically. In this case too we put emphasis on how the model dynamics evolve with the recovery rate (δ). We find that, for very small to moderate values of δ (≤ 0.6), stable solutions for all three populations are oscillatory. But, for $\delta > 0.6$, the solutions are single valued and stable. Again with $\delta \geq 1$ the system get stable single solution after small bifurcation. When recovery rate attains a threshold $\delta \sim 100$ (in units of per designated area), only the susceptible host population (S) survives asymptotically while infected host (I) and pathogen (V) populations are pushed to extinction. This feature of recovery and sustenance of the host population subsiding any pathogenic attack, in biological terms, means that the system enters a disease-free zone. Our numerical calculations show that the removal of infected host population, coupled with a finite rate of death of pathogen, actually forces the pathogen population towards extinction path. Notice that the threshold value of the recovery rate in the present case is higher than its biologically realizable value. This threshold δ can be scaled down to sensible limits provided we can set the death rate of infected host (d) to a value higher than that considered here, and also the rate of contacts (λ & γ) of S with I and V respectively to their further lower values. Actually, in a biological prototype of host-pathogen model, numerical values of the parameters d, λ, γ are externally controllable. Hence the prediction that, a disease free situation for the host population can be effected at biologically and physically realizable threshold of recovery rate, only setting the externally controllable parameters to their respective suitable values.

Numerical solution of the model equation (3.1) with the the basic model parameters set to their standard values as in Table.1. In figure 1 we study of the delay model numerically and plot the time series solutions of the model variables corresponding to three population densities, S, I and V sweeping the values of delay factor as well as δ the recovery rate. We find that delay makes the initial oscillation in the solution trajectories to persist for longer of time. However as δ increase the amplitude of oscillation reduce short of time to moves towards it stable region. Figure 8 and from Figure 9, reflects that an increasing of τ makes the oscillations to be carried further on the time scale. This is a signature of local instability inflicted by the delay in the recovery. However an increase

in the numerical value of parameter δ, the amplitude of oscillations in the solutions and reduces the time span of the persistence of oscillations. This is clearly demonstrated by the plots of different panels in Figure 8. This plots seems to signified that there is a competition between the delay factor τ and the recovery rate of infected pathogens δ for dominance within the system. For the above set of parameters (Table.1) we can evaluate the value of $\tau_0 = 7.11$. In figure 10 shows that the system undergoes a Hopf-bifurcation at the interior equilibrium point $E^*(5.38, 5.38, 5.35)$ when $\tau = \tau_0$. We observe that when $\tau < \tau_0$ the system is stable and when the value of τ crosses the critical value τ_0 the system switches a unstable condition from the stable condition.

In Numerical simulation of section 4 it has been observed that the optimal control of drug reduces with time and rapidly moves towards its optimal strategy in certain period of time. But when time is increases the optimal strategy has no effect. Again it has been observed that if the drug is used for less than 10 days the result for best treatment will appear, but if it is introduce for more than 50 days (Figure 12.) the worst condition will be reflected in treatment.

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