TWMS J. Pure Appl. Math. V.5, N.1, 2014, pp.80-95

IMPACT AND OPTIMAL CONTROL OF MOVEMENT ON A MULTIPATCH HEPATITIS C VIRUS MODEL

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Abstract. In this paper, a deterministic multipatch hepatitis C virus model is considered and analyzed. Investigated also is the existence and stability of equilibria. It is found that if 18% to 20% movement of susceptibles are allowed between patches, the disease will persist.

Keywords: hepatitis, movement, stability, optimal control.

AMS Subject Classification: 92B05, 93A30, 93C15.

1. Introduction

Hepatitis C a most common viral infection of the liver is usually caused by hepatitis C virus. Hepatitis C virus (HCV) was first identified in the year 1989. Globally, hepatitis has infected an estimated 130 million people, most of whom are chronically infected [32]. The hepatitis C virus has also been estimated to account for 27% of cirrhosis and 25% hepatocellular carcinoma, Alter (2007). Hepatitis C virus (HCV) is a liver disease caused by infection with the hepatitis C virus (HCV). This disease is spread through contacts between susceptible individuals with the blood of an infected person, and can lead to liver inflammation and scarring (fibrosis). It is estimated that 85% of the individuals exposed to HCV develop chronic hepatitis C, of which about 15% have the possibility to clear the virus spontaneously within a few months of infection. Unless the disease is successfully treated, otherwise, once a chronic stage develops HCV remains in the body [28]. It has also been suggested that having HIV may impair the clearance of HCV. For example the rate of HCV seroprevalence rate among pregnant women is estimated to be 1% (Roberts and Yeung [34]) and among the HIV infected pregnant women, the rate is as high as 30% to 50% in certain areas (Papaevangclou et al [30]). As a matter of fact, Hepatitis C virus in pregnancy is emerging and today it is becoming an increasing source of concern (Jamieson et al [13]).

Treatment for Hepatitis C does exist though, however, the current drug therapies being in use (that is, Peginterferon and Ribavirin) are ineffective in completely eradicating the disease.Unfortunately, there is no effective vaccine yet developed which may help control the spread of the disease. Efforts are already in progress for a vaccine [7] to control the disease.

Mathematical modeling of the spread of infectious diseases continues to become an important tool in understanding the dynamics of diseases and in decision making processes regarding diseases intervention programs for disease in many countries. For instance, Daozhou and Shigui [8] proposed a multipatch model to study the effects of population dispersal on the spatial spread of malaria between patches. Cai and Li [6] considered an SEI epidemic model with acute and chronic stages using Bendixon-Dulax criterion. Also Martcheva and Castillo-Chavez [23] considered a model of hepatitis C virus with chronic infectious stage in a varying population, which was extended by Yuan and Yang [40] by incorporating the latent period.

Specifically, there have been various studies of epidemiological models where optimal control methods were applied. Just to mention a few, these include Zaman et al [41] who studied

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Manuscript received August 2013.

a general SIR epidemic model and applied stability analysis theory to find the equilibrium solutions and then used optimal control to determine the optimal vaccination strategies to reduce the susceptible and infective individuals. Suresh [35] formulated and analyzed an optimal control problem with a simple epidemic model to examine the effect of a quarantine program. Gupta and Rink [12] considered the application of optimal control to find the most economical use of active and passive immunization in controlling infectious disease. Kirschner et al [17] used optimal control to examine the role of chemotherapy in controlling the virus reproduction in an HIV patient. Adam et al [1] derived HIV therapeutic strategies by formulating and analyzing an optimal control problem using two types of dynamic treatments. Wickwire [37] applied optimal control to mathematical models of pests and infectious diseases control. Marco and Takashi [22] used optimal control to study dengue disease transmission. Wiemer [38] studied Schistosomiasis using optimal control methods. Okosun et al [29] derived and analyzed a malaria disease transmission mathematical model that includes treatment and vaccination with waning immunity and applied optimal control to study the impact of a possible vaccination with treatment strategies in controlling the spread of malaria.

In this paper, we considered an $SEITV$ (susceptible, exposed, acute infected, treatment and chronic infected) model of a multipatch hepatitis C virus model. Our model is a modified and extended version of the hepatitis C virus model presented in Yuan and Yang [40] with the inclusion of treatment class, movement of susceptibles, infective, treated and chronic infected individuals between patches and time dependent control strategies, in order to determine the optimal strategy for the control of the disease.

The paper is organized as follows, in Section 2, we derive a model consisting of ordinary differential equations (ODE) that describes the interactions and the dynamics of the disease with the underlying assumptions. In Section 3, we use Pontryagin's Maximum Principle to investigate optimal strategies and to find the necessary conditions for the optimal control of the disease. In Section 4, we show the simulation results and the cost-effectiveness analysis. Our conclusions are discussed in Section 5.

2. Model formulation

The model sub-divides the total Patch 1 population at time t, denoted by $N(1)$, into the following sub-populations of susceptible individuals $S_1(t)$, individuals with acute infection $I_1(t)$, individuals undergoing treatment $T_1(t)$ and individuals with chronic infection $C_1(t)$. So that

$$N_1(t) = S_1(t) + I_1(t) + T_1(t) + C_1(t).$$

The total Patch 2 population at time t, denoted by $N_2(t)$, is sub-divided into susceptible individuals $S_2(t)$, individuals with acute infection $I_2(t)$, individuals undergoing treatment $T_2(t)$ and individuals with chronic infection $C_2(t)$. So that

$$N_2(t) = S_2(t) + I_2(t) + T_2(t) + C_2(t).$$

Susceptible individuals are recruited into Patches at a rate Λ_i $(i = 1, 2)$. The μ is the natural death rate, κ_i $(i = 1, 2)$, is the progression from acute infected class to both treatment and chronic infected class in the Patches. The term ϵ_i $(i = 1, 2)$, is the rate of progression from chronic infected class to treatment class. The transmission rate of hepatitis C (that is, the effective contact rate (ϕ_i) multiplied by the probability that transmission occurs (η_i) between individuals with acute hepatitis C, chronic hepatitis C and individuals undergoing treatment but not yet cured) are respectively $\beta_i = \phi_i\eta_i$. The rate of progression for treatment from acute infected and chronic hepatitis are π_1 and π_2 respectively. The rate of progression for treatment from acute infected and chronic hepatitis are π_1 and π_2 respectively. The term ω_j, is the proportion of acute infected, chronic and individuals on treatment who move from one Patch to the other.

Thus, putting the above formulations and assumptions together gives the following hepatitis climate model, given by system of ordinary differential equations below as

$$\begin{cases} \frac{d}{dt}S_1 = & \Lambda_1 - \mu S_1 - \beta_1 S_1(I_1 + T_1 + C_1) + \rho_1 T_1 + \omega_{S_2} S_2 \\ \frac{d}{dt}I_1 = & \beta_1 S_1(I_1 + T_1 + C_1) - (\kappa_1 + \mu)I_1 + \omega_{I_2} I_2 \\ \frac{d}{dt}T_1 = & \pi_1\kappa_1 I_1 + \epsilon_1 C_1 - (\rho_1 + \mu)T_1 + \omega_{T_2} T_2 \\ \frac{d}{dt}C_1 = & (1-\pi_1)\kappa_1 I_1 - (\epsilon_1 + \mu)C_1 + \omega_{C_2} C_2 \\ \\ \frac{d}{dt}S_2 = & \Lambda_2 - \mu S_2 - \beta_2 S_2(I_2 + T_2 + C_2) + \rho_2 T_2 + \omega_{S_1} S_1 \\ \frac{d}{dt}I_2 = & \beta_2 S_2(I_2 + T_2 + C_2) - (\kappa_2 + \mu)I_2 + \omega_{I_1} I_1 \\ \frac{d}{dt}T_2 = & \pi_2\kappa_2 I_2 + \epsilon_2 C_2 - (\rho_2 + \mu)T_2 + \omega_{T_1} T_1 \\ \frac{d}{dt}C_2 = & (1-\pi_2)\kappa_2 I_2 - (\epsilon_2 + \mu)C_2 + \omega_{C_1} C_1 \end{cases} \tag{1}$$

2.1. **Stability of the disease-free equilibrium (DFE).** The single Hepatitis model (1) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$E_0 = (S_1^*, I_1^*, T_1^*, C_1^*, S_2^*, I_2^*, T_2^*, C_2^*) = \left(\frac{\Lambda_1 + \omega_{S_2} S_2^*}{\mu}, 0, 0, 0, \frac{\Lambda_2 + \omega_{S_1} S_1^*}{\mu}, 0, 0, 0\right).$$

The linear stability of E_0 can be established using the next generation operator method in Driessche and Watmough [9] on the system (1), the matrices F and Ψ, for the new infection terms and the remaining transfer terms, are, respectively, given by,

It follows that the reproduction number of the Hepatitis model (1), denoted by R_0, is given by

$$R_0 = \max\{R_1, R_2\},$$

where

$$\begin{aligned} R_1 &= S_1^*\beta_1\left(\frac{(\mu+\epsilon_1)(\mu+\kappa_1) + (\mu+\epsilon_1+\kappa_1(1-\pi_1))\rho_1}{(\mu+\epsilon_1)(\mu+\kappa_1)(\mu+\rho_1)}\right), \\ R_2 &= S_2^*\beta_2\left(\frac{(\mu+\epsilon_2)(\mu+\kappa_2) + (\mu+\epsilon_2+\kappa_2(1-\pi_2))\rho_2}{(\mu+\epsilon_2)(\mu+\kappa_2)(\mu+\rho_2)}\right). \end{aligned} \tag{2}$$

Further, using Theorem 2 in Driessche and Watmough [9], the following result is established. The DFE is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

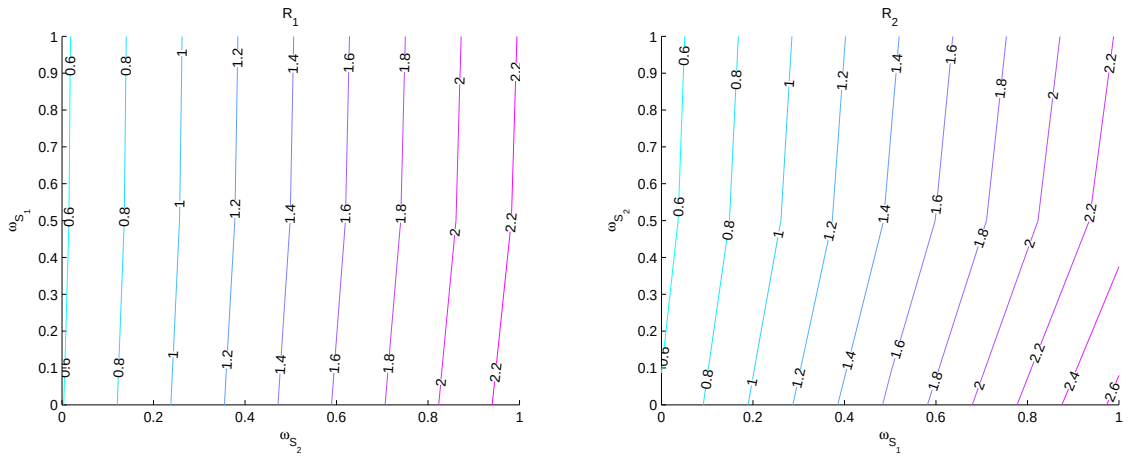

Figure 1. Simulation of the model showing contour plots of R_1 and R_2 as a function of movement terms ω_{S_1} and ω_{S_2}. Parameter values used in simulation is as shown in Table 1.

Figure 1 show the contour plots of the reproductive numbers a of patch 1 and patch 2 respectively, this simulation suggest that the disease will persist in patch 1 if at least 20%

movement of susceptibles from patch 2 is allowed into patch 1, and similarly, the disease will persist in patch 2 if at least 18% movement of susceptibles from patch 1 is allowed into patch 2.

3. Analysis of optimal control

In the this section, we apply optimal control method using Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the Hepatitis disease. We incorporate time dependent controls into the model (1) to determine the optimal strategy for controlling the disease. Hence, we have,

$$\begin{cases} \frac{d}{dt}S_1 = & \Lambda_1 - \mu S_1 - \beta_1 S_1(I_1+T_1+C_1) + \rho_1 T_1 + \omega_{S_2} S_2 \\ \frac{d}{dt}I_1 = & \beta_1 S_1(I_1+T_1+C_1) - (u_3\kappa_1+\mu)I_1 + (1-u_2)\omega_{I_2} I_2 \\ \frac{d}{dt}T_1 = & u_3\pi_1\kappa_1 I_1 + u_4\epsilon_1 C_1 - (\rho_1+\mu)T_1 + (1-u_2)\omega_{T_2} T_2 \\ \frac{d}{dt}C_1 = & u_3(1-\pi_1)\kappa_1 I_1 - (u_4\epsilon_1+\mu)C_1 + (1-u_2)\omega_{C_2} C_2 \\ \\ \frac{d}{dt}S_2 = & \Lambda_2 - \mu S_2 - \beta_2 S_2(I_2+T_2+C_2) + \rho_2 T_2 + \omega_{S_1} S_1 \\ \frac{d}{dt}I_2 = & \beta_2 S_2(I_2+T_2+C_2) - (u_3\kappa_2+\mu)I_2 + (1-u_1)\omega_{I_1} I_1 \\ \frac{d}{dt}T_2 = & u_3\pi_2\kappa_2 I_2 + u_4\epsilon_2 C_2 - (\rho_2+\mu)T_2 + (1-u_1)\omega_{T_1} T_1 \\ \frac{d}{dt}C_2 = & u_3(1-\pi_2)\kappa_2 I_2 - (u_4\epsilon_2+\mu)C_2 + (1-u_1)\omega_{C_1} C_1 \end{cases} \tag{3}$$

The control functions, $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$ are bounded, Lebesgue integrable functions. The control $u_1(t)$ represents the effort from Patch 1 on screening of movement of acute infected (ω_{I_1}), chronic (ω_{C_1}) and individuals on treatment (ω_{I_1}) to reduce the movement of individuals that may be infectious into Patch 2. The control $u_2(t)$ represents the effort from Patch 2 on screening of movement of acute infected (ω_{I_2}), chronic (ω_{C_2}) and individuals on treatment (ω_{I_2}) to reduce the movement of individuals that may be infectious into Patch 1.

The control on treatment $u_3(t)$ satisfies $0 \leqslant u_3 \leqslant g_2$, where g_2 is the drug efficacy use for treatment of acutely infected individuals. The control on treatment of chronic infected individuals $u_4(t)$ satisfies $0 \leqslant u_3 \leqslant g_3$, where g_3 is the drug efficacy use for treatment of chronic infected individuals. Our control problem involves a situation in which the number of infectious individuals, those with acute infections and the cost of applying screening and treatment controls $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$ are minimized subject to the system (3). The objective functional is defined as:

$$J = \min_{u_1,u_2,u_3} \int_0^{t_f} [A_1 I_1 + A_2 I_2 + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + B_4 u_4^2] dt, \tag{4}$$

where t_f is the final time and the coefficients, $A_1, A_2, B_1, B_2, B_3, B_4$ are balancing cost factors due to scales and importance of the five parts of the objective function. We seek to find an optimal control, u_1^*, u_2^*, u_3^*, and u_4^* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min\{J(u_1,u_2,u_3,u_4) | u_1,u_2,u_3,u_4 \in \mathcal{U}\}, \tag{5}$$

where $\mathcal{U} = \{(u_1,u_2,u_3,u_4)$ such that u_1,u_2,u_3,u_4 are measurable with $0 \leq u_1 \leq 1$, $0 \leq u_2 \leq 1, 0 \leq u_3 \leq g_2$ and $0 \leq u_4 \leq g_3$, for $t \in [0,t_f]\}$ is the control set. The necessary conditions that an optimal solution must satisfy come from the Pontryagin et al [31] Maximum Principle. This principle converts (3)-(4) into a problem of minimizing pointwise a Hamiltonian

H, with respect to u_1, u_2, u_3 and u_4

$$\begin{aligned} H &= A_1I_1 + A_2I_2 + B_1u_1^2 + B_2u_2^2 + B_3u_3^2 + B_4u_4^2 + \\ &+M_{S_1}\{[\Lambda_1 - \mu S_1 - \beta_1 S_1(I_1 + T_1 + C_1) + \rho_1 T_1 + \omega_{S_2} S_2\} + \\ &+M_{I_1}\{\beta_1 S_1(I_1 + T_1 + C_1) - (u_3\kappa_1 + \mu)I_1 + (1 - u_2)\omega_{I_2} I_2\} + \\ &+M_{T_1}\{u_3\pi_1\kappa_1 I_1 + u_4\epsilon_1 C_1 - (\rho_1 + \mu)T_1 + (1 - u_2)\omega_{T_2} T_2\} + \\ &+M_{C_1}\{u_3(1 - \pi_1)\kappa_1 I_1 - (u_4\epsilon_1 + \mu)C_1 + (1 - u_2)\omega_{C_2} C_2\} + \\ &+M_{S_2}\{\Lambda_2 - \mu S_2 - \beta_2 S_2(I_2 + T_2 + C_2) + \rho_2 T_2 + \omega_{S_1} S_1\} + \\ &+M_{I_2}\{\beta_2 S_2(I_2 + T_2 + C_2) - (u_3\kappa_2 + \mu)I_2 + (1 - u_1)\omega_{I_1} I_1\} + \\ &+M_{T_2}\{u_3\pi_2\kappa_2 I_2 + u_4\epsilon_2 C_2 - (\rho_2 + \mu)T_2 + (1 - u_1)\omega_{T_1} T_1\} + \\ &+M_{C_2}\{u_3(1 - \pi_2)\kappa_2 I_2 - (u_4\epsilon_2 + \mu)C_2 + (1 - u_1)\omega_{C_1} C_1\}, \end{aligned} \tag{6}$$

where the $M_{S_1}, M_{I_1}, M_{T_1}, M_{C_1}, M_{S_2}, M_{I_2}, M_{T_2}$ and M_{C_2} are the adjoint variables or co-state variables. The system of equations is found by taking the appropriate partial derivatives of the Hamiltonian (6) with respect to the associated state variable.

Theorem 3.1. *Given optimal control $u_1^*, u_2^*, u_3^*, u_4^*$ and solutions $S_1, I_1, T_1, C_1, S_2, I_2, T_2, C_2$ of the corresponding state system (3)- (4) that minimize $J(u_1, u_2, u_3, u_4)$ over U. Then there exists adjoint variables $M_{S_1}, M_{I_1}, M_{T_1}, M_{C_1}, M_{S_2}, M_{I_2}, M_{T_2}, M_{C_2}$ satisfying*

$$\frac{-dM_i}{dt} = \frac{\partial H}{\partial i}, \tag{7}$$

where $i = S_1, I_1, T_1, C_1, S_2, I_2, T_2, C_2$ and with transversality conditions

$$M_{S_1}(t_f) = M_{I_1}(t_f) = M_{T_1}(t_f) = M_{C_1}(t_f) = M_{S_2}(t_f) = M_{I_2}(t_f) = M_{T_2}(t_f) = M_{C_2}(t_f) = 0, \tag{8}$$

$$u_1^* = \min\left\{1, \max\left(0, \frac{M_{I_2}\omega_{I_2} I_1 + M_{T_2}\omega_{T_2} T_1 + M_{C_2}\omega_{C_2} C_1}{2B_1}\right)\right\}, \tag{9}$$

$$u_2^* = \min\left\{1, \max\left(0, \frac{M_{I_1}\omega_{I_2} I_2 + M_{T_1}\omega_{T_1} T_2 + M_{C_1}\omega_{C_1} C_2}{2B_2}\right)\right\}, \tag{10}$$

$$u_3^* = \min\left\{1, \max\left(0, \frac{\kappa_1 I_1(M_{I_1} - M_{C_1}) + \pi_1\kappa_1 I_1(M_{C_1} - M_{T_1}) + Q}{2B_3}\right)\right\}, \tag{11}$$

and

$$u_4^* = \min\left\{1, \max\left(0, \frac{\epsilon_1 C_1(M_{C_1} - M_{T_1}) + \epsilon_2 C_2(M_{C_2} - M_{T_2})}{2B_4}\right)\right\}, \tag{12}$$

where $Q = \kappa_2 I_2(M_{I_2} - M_{C_2}) + \pi_2\kappa_2 I_2(M_{C_2} - M_{T_2})$.

Proof. Corollary 4.1 of Fleming and Rishel [11] gives the existence of an optimal control due to the convexity of the integrand of J with respect to u_1, u_2, u_3 and u_4, a *priori* boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint equations can be

written as

$$\begin{aligned}
-\frac{dM_{S_1}}{dt} &= \mu M_{S_1} + (M_{S_1} - M_{I_1})\beta_1(I_1 + T_1 + C_1) - M_{S_2}\omega_{S_2},\\
-\frac{dM_{I_1}}{dt} &= -A_1 + (M_{S_1} - M_{I_1})\beta_1 S_1 + u_3\kappa_1(M_{I_1} - M_{C_1}) + u_3\pi_1\kappa_1(M_{C_1} - M_{T_1})\\
&\quad + \mu M_{I_1} - (1-u_1)\omega_{I_2}M_{I_2},\\
-\frac{dM_{T_1}}{dt} &= (M_{S_1} - M_{I_1})\beta_1 S_1 - \rho_1 M_{S_1} + (\rho_1 + \mu)M_{T_1} - (1-u_1)\omega_{T_2}M_{T_2},\\
-\frac{dM_{C_1}}{dt} &= (M_{S_1} - M_{I_1})\beta_1 S_1 - u_4\epsilon_1 M_{T_1} + (u_4\epsilon_1 + \mu)M_{C_1} - (1-u_1)\omega_{C_2}M_{C_2},\\
-\frac{dM_{S_2}}{dt} &= -M_{S_1}\omega_{S_1} + M_{S_2}\mu + (M_{S_2} - M_{I_2})\beta_2(I_2 + T_2 + C_2),\\
-\frac{dM_{I_2}}{dt} &= -A_2 - (1-u_2)\omega_{I_1}M_{I_1} + \beta_2 S_2(M_{S_2} - M_{I_2}) + M_{I_2}(u_3\kappa_2 + \mu)\\
&\quad - M_{T_2}u_3\pi_2\kappa_2 - M_{C_2}u_3(1-\pi_2)\kappa_2,\\
-\frac{dM_{T_2}}{dt} &= -M_{T_1}(1-u_2)\omega_{T_1} + (M_{S_2} - M_{I_2})\beta_2 S_2 - \rho_2 M_{S_2} + M_{T_2}(\rho_2 + \mu),\\
-\frac{dM_{C_2}}{dt} &= \beta_2 S_2(M_{S_2} - M_{I_2}) - M_{C_1}(1-u_2)\omega_{C_1} - u_4\epsilon_2 M_{T_2} + M_{C_2}(u_4\epsilon_2 + \mu).
\end{aligned} \tag{13}$$

Solving for u_1^*, u_2^* and u_3^* subject to the constraints, the characterization (9-11) can be derived and we have

$$\begin{aligned}
0 = \frac{\partial H}{\partial u_1} &= 2B_1u_1 - M_{I_2}\omega_{I_2}I_1 - M_{T_2}\omega_{T_2}T_1 - M_{C_2}\omega_{C_2}C_1,\\
0 = \frac{\partial H}{\partial u_2} &= 2B_2u_2 - M_{I_1}\omega_{I_2}I_2 - M_{T_1}\omega_{T_1}T_2 - M_{C_1}\omega_{C_1}C_2,\\
0 = \frac{\partial H}{\partial u_3} &= 2B_3u_3 - \kappa_1 I_1(M_{I_1} - M_{C_1}) - \pi_1\kappa_1 I_1(M_{C_1} - M_{T_1}) - Q,\\
0 = \frac{\partial H}{\partial u_4} &= 2B_4u_4 - \epsilon_1 C_1(M_{C_1} - M_{T_1}) - \epsilon_2 C_2(M_{C_2} - M_{T_2}).
\end{aligned} \tag{14}$$

Hence, we obtain (see Lenhart and Workman (2007))

$$\begin{aligned}
u_1^* &= \frac{M_{I_2}\omega_{I_2}I_1 + M_{T_2}\omega_{T_2}T_1 + M_{C_2}\omega_{C_2}C_1}{2B_1},\\
u_2^* &= \frac{M_{I_1}\omega_{I_2}I_2 + M_{T_1}\omega_{T_1}T_2 + M_{C_1}\omega_{C_1}C_2}{2B_2},\\
u_3^* &= \frac{\kappa_1 I_1(M_{I_1} - M_{C_1}) + \pi_1\kappa_1 I_1(M_{C_1} - M_{T_1}) + Q}{2B_3},\\
u_4^* &= \frac{\epsilon_1 C_1(M_{C_1} - M_{T_1}) + \epsilon_2 C_2(M_{C_2} - M_{T_2})}{2B_4}.
\end{aligned} \tag{15}$$

By standard control arguments involving the bounds on the controls, we conclude

$$u_1^* = \begin{cases} 0 & \text{If } \xi_1^* \le 0\\ \xi_1^* & \text{If } 0 < \xi_1^* < 1\\ 1 & \text{If } \xi_1^* \ge 1, \end{cases}$$

$$u_2^* = \begin{cases} 0 & \text{If } \xi_2^* \le 0\\ \xi_2^* & \text{If } 0 < \xi_2^* < 1\\ 1 & \text{If } \xi_2^* \ge 1, \end{cases}$$

$$u_3^* = \begin{cases} 0 & \text{If } \xi_3^* \le 0\\ \xi_3^* & \text{If } 0 < \xi_3^* < 1\\ 1 & \text{If } \xi_3^* \ge 1, \end{cases}$$

$$u_4^* = \begin{cases} 0 & \text{If } \xi_4^* \leq 0 \\ \xi_4^* & \text{If } 0 < \xi_4^* < 1 \\ 1 & \text{If } \xi_4^* \geq 1, \end{cases}$$

where

$$\xi_1^* = \frac{M_{I_2}\omega_{I_2}I_1 + M_{T_2}\omega_{T_2}T_1 + M_{C_2}\omega_{C_2}C_1}{2B_1},$$

$$\xi_2^* = \frac{M_{I_1}\omega_{I_2}I_2 + M_{T_1}\omega_{T_1}T_2 + M_{C_1}\omega_{C_1}C_2}{2B_2},$$

$$\xi_3^* = \frac{\kappa_1 I_1(M_{I_1} - M_{C_1}) + \pi_1\kappa_1 I_1(M_{C_1} - M_{T_1}) + Q}{2B_3},$$

$$\xi_4^* = \frac{\epsilon_1 C_1(M_{C_1} - M_{T_1}) + \epsilon_2 C_2(M_{C_2} - M_{T_2})}{2B_4}.$$

□

Next, we discuss the numerical solutions of the optimality system and the corresponding results of varying the optimal controls u_1, u_2, u_3 and u_4, the parameter choices, and the interpretations from various cases.

4. Numerical results and discussions

In this section, we investigate numerically the effect of the following itemized optimal control strategies listed below on the spread of hepatitis C virus in the two population. The optimal control solution is obtained by solving the optimality system, which consists of the state system and the adjoint system. An iterative scheme is used for solving the optimality system. We begin by solving the state equations with a guess for the controls over the simulated time using the fourth order Runge-Kutta scheme. Because of the transversality conditions (8), the adjoint equations are solved by the backward fourth order Runge-Kutta scheme using the current iterations solutions of the state equations. Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (9) - (13). This process is repeated and the iterations are stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iteration ([2, 3, 18, 19])

We have chosen the same set of the weight factors, $A_1 = 950$, $A_2 = 800$, $B_1 = 600$, $B_2 = 600$, $A_3 = 800$, $A_4 = 850$ and same initial state variables $S_1(0) = 800$, $I_1(0) = 10$, $T_1(0) = 50$, $C_1(0) = 50$, $S_2(0) = 750$, $I_2(0) = 10$, $T_2(0) = 40$ and $C_2(0) = 10$ to illustrate the effect of different optimal control strategies on the spread of the disease.

Table 1. Values of parameters used in the numerical simulation.

Parameter	Value(range)	Units	Source
Λ_1, Λ_2	85	per year	[24, 25]
μ	0.085	per year	[24, 25]
β_1, β_2	(0,1)	per year	[24, 25]
π_1, π_2	0.24 - 0.27	-	[24, 25]
ρ	1.992	per year	[25]
ψ	(0,1]	-	Variable
ϵ_1	0.06	-	Assumed
b	0.4	-	Assumed
κ_1, κ_2	0.5 - 0.7	-	Assumed
ϵ_2	0.05	-	Assumed

Strategy A: Optimal restriction of movement of infectives without treatments. In Figure 4, the movement restrictions control (u_1 and u_2) are used to optimize the objective function (J) while we set the treatment of acute infected (u_3) and chronic infected control (u_4) to zero. We observe that in patch 1, Figure 4(a-b), the number of acute infected (I) and chronic infected individuals decreases significantly compared with the case without control, while in patch 2 Figure 4(c-d), there is only a significant decrease in the number of chronic infected individuals. The control profile is shown in Figure 4(e).

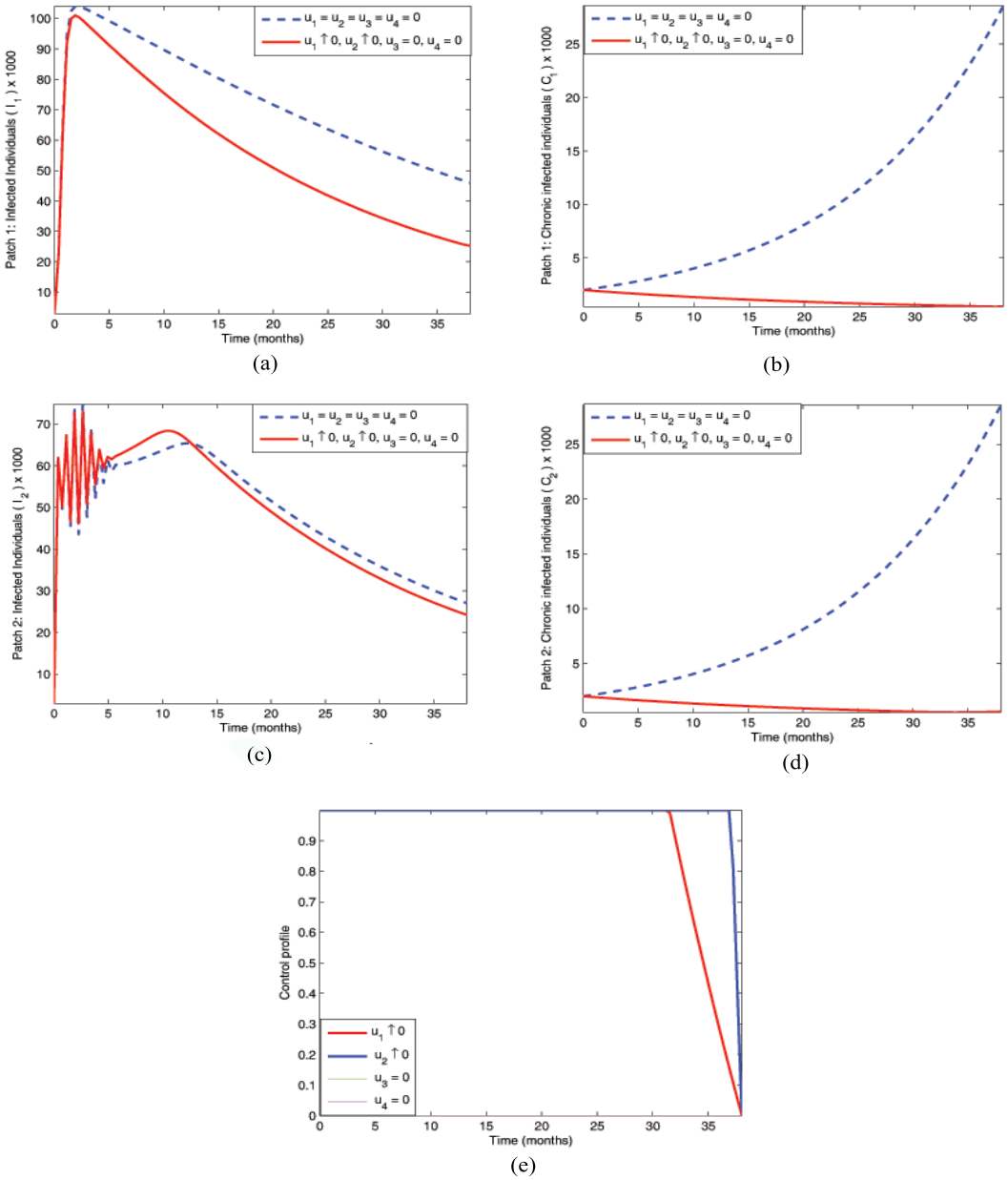

Figure 2. Simulations of the hepatitis C virus model

Strategy B: Optimal treatment of infectives without restriction of movements. In Figure 4, the treatment of acute infected (u_3) and chronic infected control (u_4) are used to optimize the objective function (J) while we set the movement restrictions control (u_1 and u_2) to zero. We observe that in patch 1, Figure 4(a-b) there is no significant reduction in the number of acute infected (I) and the chronic infected individuals indicates an increase in time.

Similar scenario is observed in patch 2 Figure 4(c-d). The control profile is shown in Figure 4(e). This strategy clearly show the impact of unrestricted movement of infectives on the disease transmission.

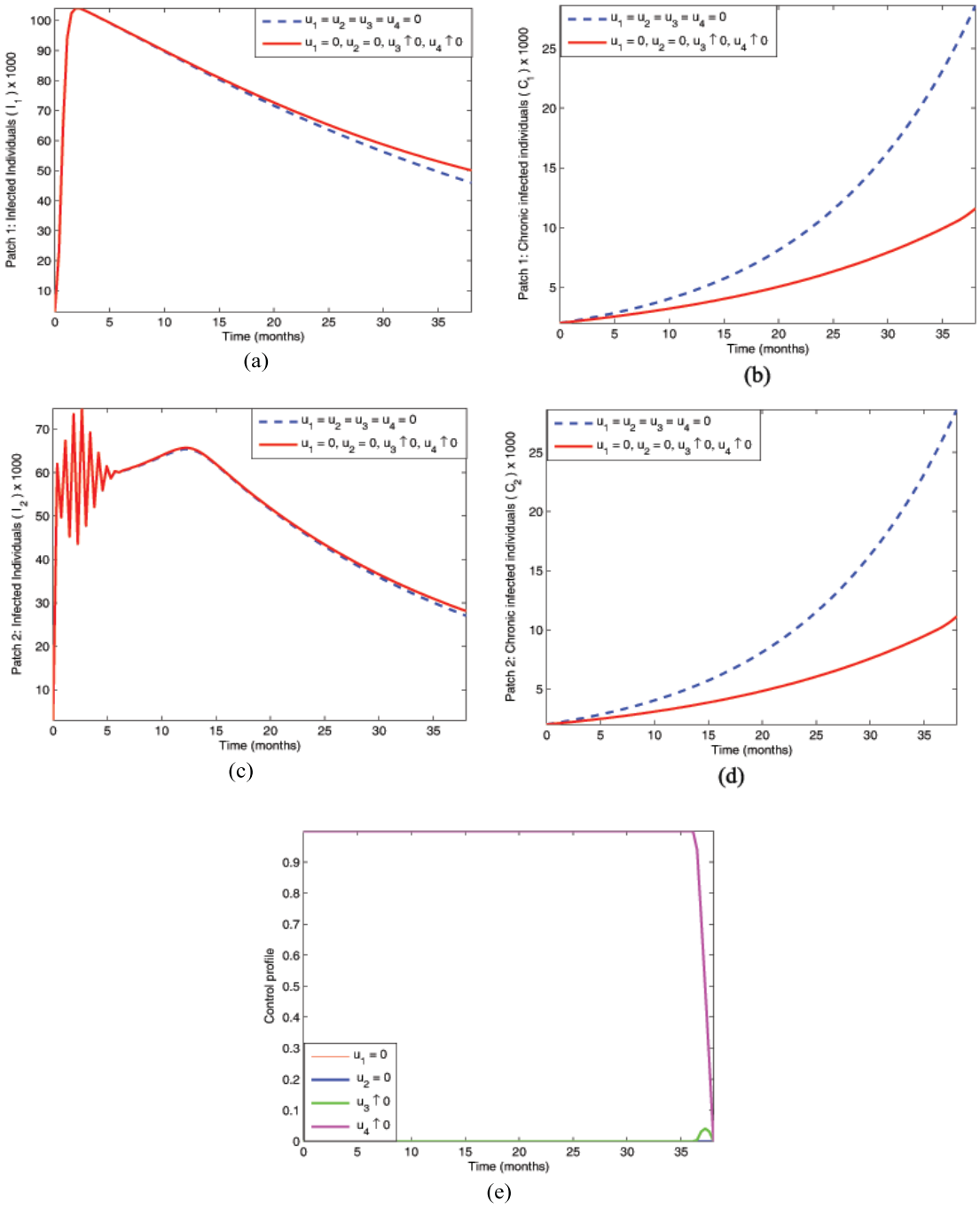

Figure 3. Simulations of the hepatitis C virus model

Strategy C: Optimal treatment and restriction of movement of infectives only from patch (population) 1. In Figure 4, the movement restriction (u_1) on patch 1, treatment of acute infected (u_3) and chronic infected control (u_4) are used to optimize the objective function (J) while we set the movement restrictions control (u_2) to zero. We observe that in patch 1, Figure 4(a-b) there is no significant reduction in the number of acute infected (I) and the chronic

infected individuals indicates significant decrease in time. However, in patch 2 Figure 4(c-d), we observed a significant difference in the number of acute infected (I) with optimal control compared to the case without control and the chronic infected individuals indicates significant decrease in time. The control profile is shown in Figure 4(e). This strategy clearly show the impact of unrestricted movement of infectives from patch 2 on the disease transmission.

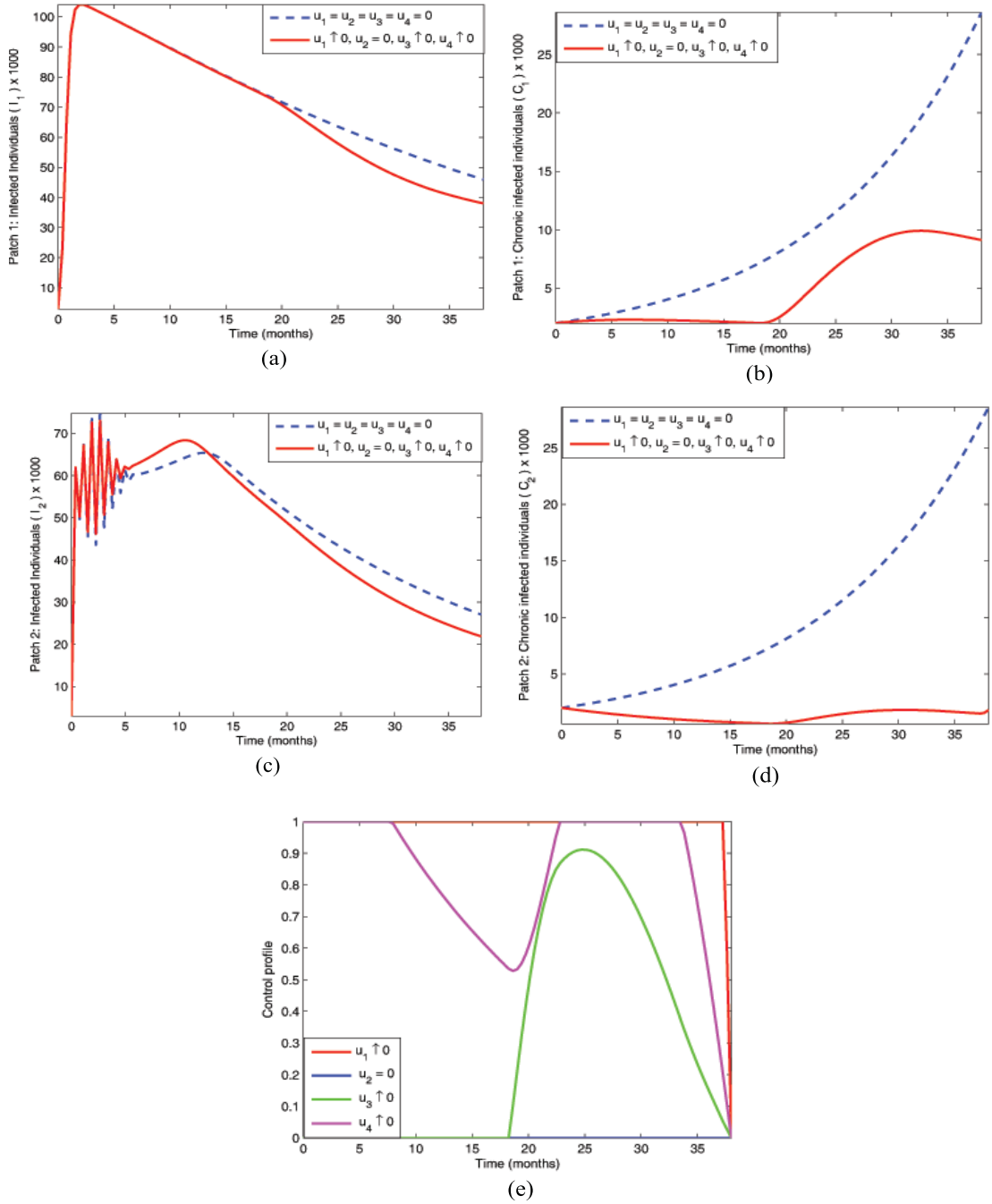

Figure 4. Simulations of the hepatitis C virus model

Strategy D: Optimal treatment and restriction of movement of infectives only from patch (population) 2. In Figure 4, the movement restriction (u_2) on patch 2, treatment of acute infected (u_3) and chronic infected control (u_4) are used to optimize the objective function

(J) while we set the movement restrictions control (u_1) to zero. We observed that in patch 1, Figure 4(a-b) there is significant reduction in the number of acute infected (I) and the chronic infected individuals indicates significant decrease in time. Also, in patch 2 Figure 4(c-d), we observed no significant difference in the number of acute infected (I) with optimal control compared to the case without control and the chronic infected individuals indicates significant decrease in time.

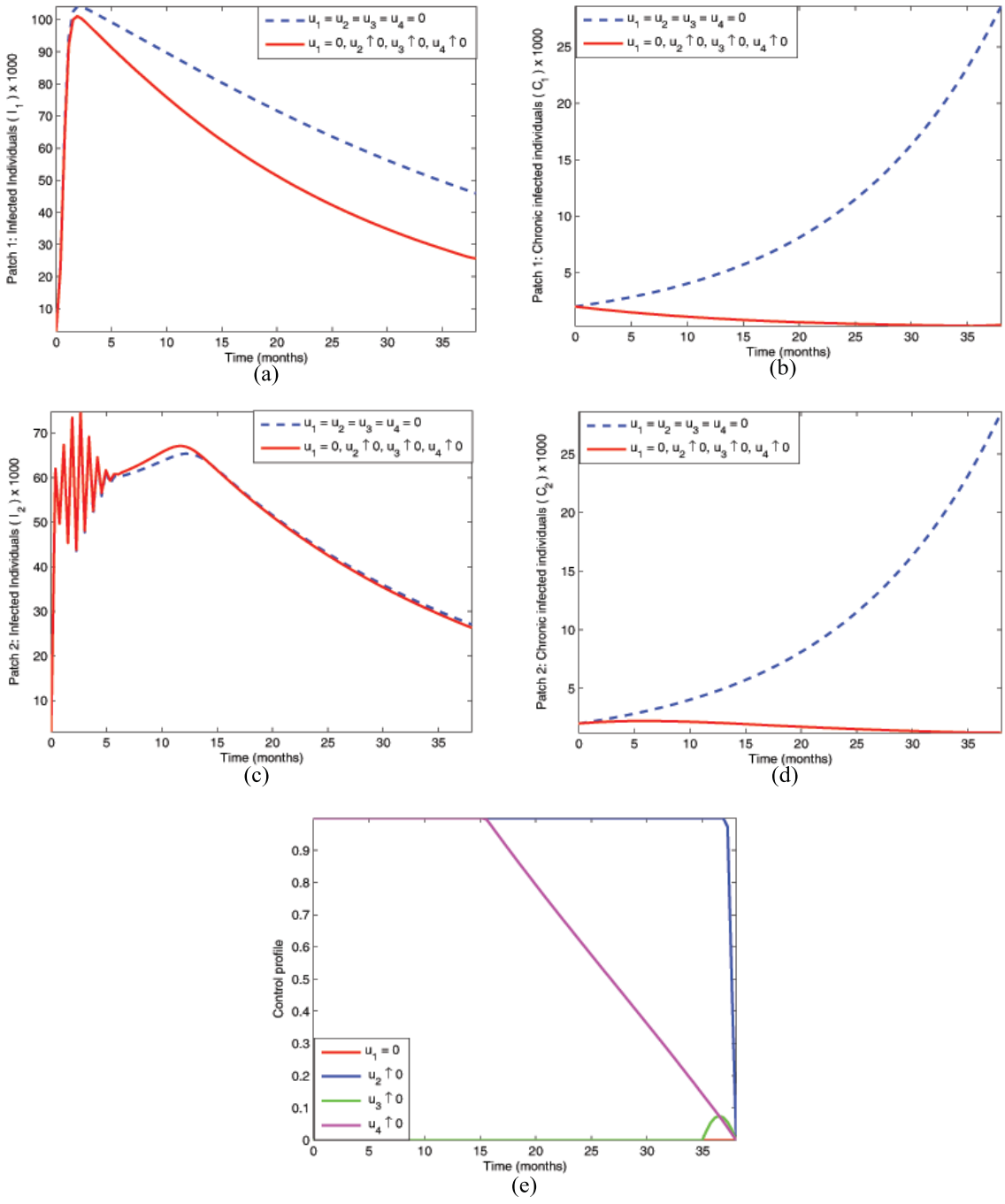

Figure 5. Simulations of the hepatitis C virus model

The control profile is shown in Figure 4(e). This strategy clearly show the impact of unrestricted movement of infectives from patch 1 on the disease transmission.

Strategy E: Optimal treatment and restriction of movement of infectives from both patches (populations). In Figure 4, the movement restrictions (u_1 and u_2) on patches 1 and 2, treatment of acute infected (u_3) and chronic infected control (u_4) are all used to optimize the objective function (J). We observe that in patch 1, Figure 4(a-b) there is significant reduction in the number of acute infected (I) and the chronic infected individuals indicates significant decrease over time.

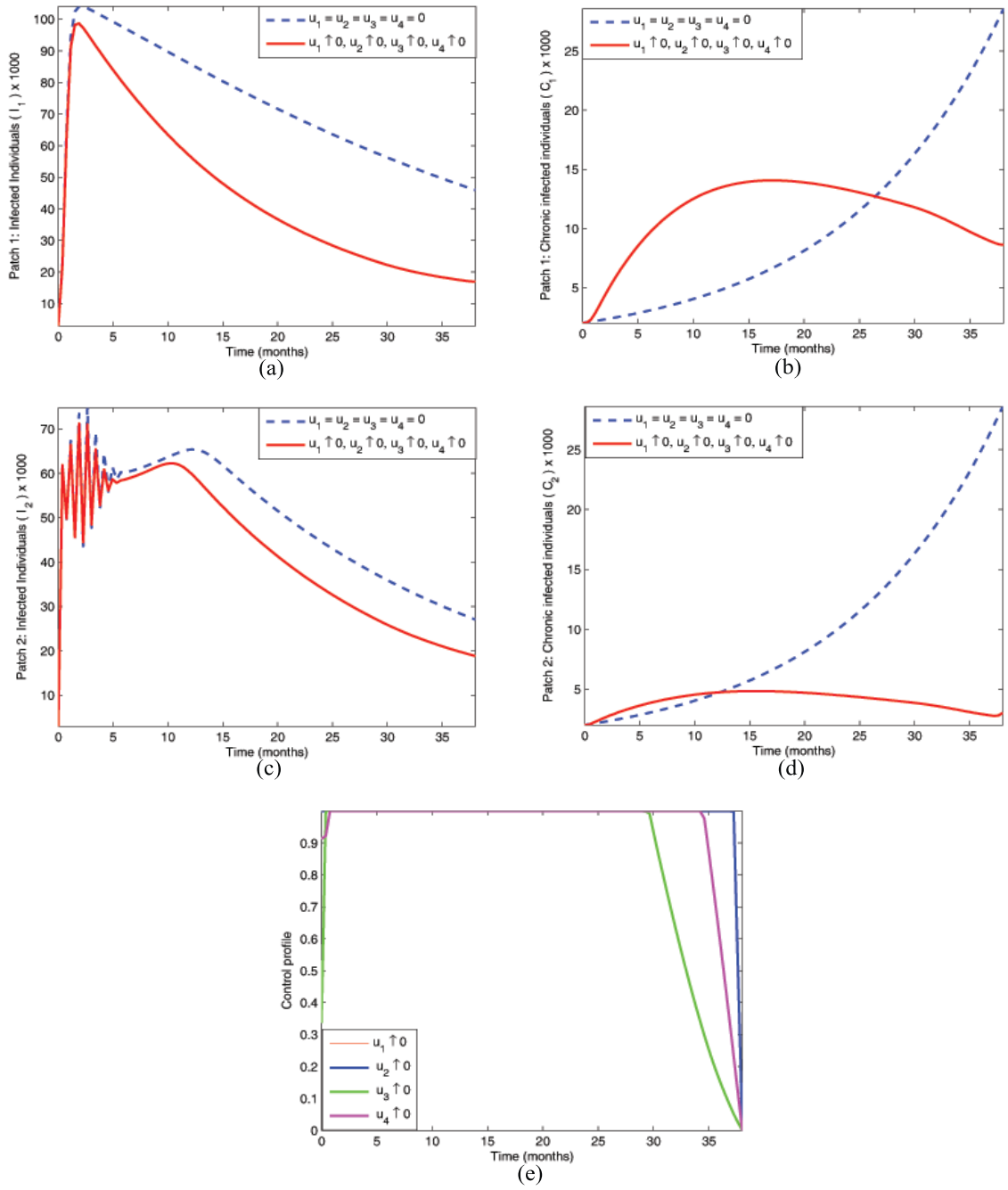

Figure 6. Simulations of the hepatitis C virus model

However, in patch 2 Figure 4(c-d), we observed a significant difference in the number of acute infected (I) with optimal control compared to the case without control and the chronic infected individuals indicates significant decrease in time. The control profile is shown in Figure 4(e).

In Figure 4 the simulation shows the effects of varying the proportion of acute infected individuals who move from patch 2 to patch 1 on the total number of infected individuals in patch 1 with optimal control and without control.

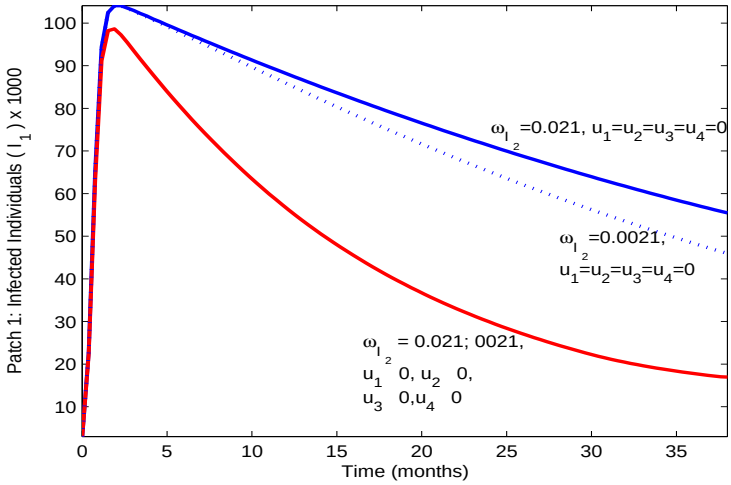

Figure 7. Simulation showing the impact of movement of infectives from patch 2 on patch 1 when there is optimal control and without control

4.1. **Cost-effectiveness analysis.** The difference between the total infectious individuals without control and the total infectious individuals with control was used to determine the "no of infection averted" term in IAR formula. Using the parameter values as in table 1, the combination of controls yielding maximum IAR was determined for each intervention strategy.

From Figures 4 and 4, one can see that the most cost-effective strategy in-terms of IAR and total costs of interventions is the combination of treatment of infective individuals and spray of insecticides. However, for more clarity, we examine the cost effectiveness ratio of the strategies, so that we can draw our conclusions.

For the purpose of our study, we consider the incremental cost-effectiveness ratio (ICER). It allows us to compare the cost-effectiveness of combination of at least two of the control strategies, use of treatment of infective individuals and movement restrictions. Based on the model simulation results, we rank the strategies in order of increasing effectiveness.

Strategies	Total infection averted	Total costs ($)	ICER
No Strategy	0	0	–
Strategy B	784.81	$7789.9	9.9258
Strategy A	3631.3	$193880	65.3753
Strategy E	4025.4	$345910	385.765

The ICER, is calculated as follows:

$$\begin{aligned}
\text{ICER(C)} &= \tfrac{7789.9}{784.81} = 9.9258,\\
\text{ICER(A)} &= \tfrac{193880-7789.9}{3631.3-784.81} = 65.3753,\\
\text{ICER(B)} &= \tfrac{345910-193880}{4025.4-3631.3} = 385.765.
\end{aligned}$$

The comparison between strategies B and A shows a cost saving of $9.9258 for strategy B over strategy A. The lower ICER for strategy B indicates that strategy A is "strongly dominated".

That is, strategy A is more costly and less effective than strategy B. Therefore, strategy A is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs ($)	ICER
Strategy B	784.81	$7789.9	9.9258
Strategy E	4025.4	$345910	104.3391

The comparison between strategies B and E shows a cost saving of $9.9258 for strategy B over strategy E. Similarly, the high ICER for strategy E indicates that strategy E is "strongly dominated". That is, strategy E is more costly and less effective than strategy B. Therefore, strategy E is excluded from the set of alternatives so it does not consume limited resources. With this result, we conclude that strategy B (Optimal treatment of infective individuals and without restriction of movements) has the least ICER and therefore is more cost-effective than strategy E.

5. Conclusions

In this paper, a deterministic multipatch hepatitis C virus model is considered in order to study the impact of movement between the patches and optimal control movement of infectives and treatments on the transmission dynamics of the disease. Derived also is the condition in which disease-free equilibrium is locally asymptotically stable and established that a stable disease-free equilibrium can only be achieved in the absence of movement of infectives. From the contour plots of the reproductive numbers a of patch 1 and patch 2 respectively, we found that the disease will persist in patch 1 if at least 20% movement of susceptibles from patch 2 is allowed into patch 1, and similarly, the disease will persist in patch 2 if at least 18% movement of susceptibles from patch 1 is allowed into patch 2. Furthermore, the impact of control mechanism on each individual population is investigated. The costs associated with each of these strategies are also investigated by formulating the costs function problem as an optimal control problem and then use the Pontryagin's Maximum Principle to solve the optimal control problems. The cost-effectiveness analysis was also investigated to determine which control strategy is most cost-effetive. From the results, it is found that optimal treatment of infective individuals and without restriction of movements strategy is most cost-effective strategy of all strategies considered.

References

[1] Adams, B.M., Banks, H.T., Kwon, H., Tran, H.T., (2004), Dynamic multidrug therapies for HIV: Optimal and STI control approaches, Mathematical Biosciences and Engineering, 1(2), pp.223-241.

[2] Agusto, F.B., (2009), Optimal chemoprophylaxis and treatment control strategies of a tuberculosis transmission model. World Journal of Modelling and Simulation, 5(3), pp.163-173.

[3] Agusto, F.B., Okosun, K.O., (2010), Optimal seasonal biocontrol for Eichhornia crassipes. International Journal of Biomathematics, 3(3), pp.383-397. 10.1142/S1793524510001021

[4] Alter, M.J., (2007), Epidemiology of hepatitis C virus infection. World Journal of Gastroenterology, 13(7), pp.2436-2441.

[5] Blayneh, K.W., Cao, Y., Kwon, H.D., (2009), Optimal control of vector-borne diseases: Treatment and Prevention, Discrete and continuous dynamical systems series B, 11(3), pp.587-611.

[6] Cai, L., Li, X., (2007), A note on global stability of an SEI epidemic model with acute and chronic stages, Appli. Math. Comput. doi:10.1016/j.amc.2007.07.024.

[7] Chen, J.Y., Li, F., (2006), Development of hepatitis C virus vaccine using hepatitis B core antigen as immuno-carrier, World J Gastroenterol, 12, pp.7774-7778.

[8] Daozhou, G., Shigui, R., (2012), A multipatch malaria model with logistic growth populations, SIAM J. Appl. Math., 72(3), pp.819-841.

[9] van Driessche, P.D., Watmough, J., (2002), Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci, 180, pp.29-48.
[10] Felippe de Souza, J.A.M., Marco, A.L.C., Takashi, Y., (2004), Optimal control Theory Applied to the Anti-Viral Treatment of AIDS, Proc. of Conference on Decision and Control, Sydney.
[11] Fleming, W.H., Rishel, R.W., (1975), Deterministic and stochastic optimal control, Springer Verlag, New York.
[12] Gupta, N. K., Rink, R. E., (1973), Optimal control of epidemics. Mathematical Biosciences. 18, 383 - 396.
[13] Jamieson, D.J., Skunodom, N., Chaowanachan, T., et.al., (2008), Infection with hepatitis C virus among HIV-infected pregnant women in Thailand. Infectious Disease in Obstetrics and Gynecology, doi:10.1155/2008/840948.
[14] Joshi, H.R., Lenhart, S., Li, M.Y., Wang, L., (2006), Optimal control methods applied to disease models, Comtemporary Mathematics, 410, pp.187-207.
[15] Joshi, H.R., (2002), Optimal Control of an HIV Immunology Model, Optim. Control Appl. Math., 23, pp.199-213.
[16] Jung, E., Lenhart, S., Feng, Z., (2002), Optimal control of treatments in a two-strain Tuberculosis model, Discrete and Continuous Dynamical Systems series B, 2(4), pp.473-482.
[17] Karrakchou, R.M., Gourari, S., (2006), Optimal control and infectiology: Application to an HIV/ AIDS model, Applied Mathematics and Computation 177, pp.807-818.
[18] Kirschner, D., Lenhart, S., Serbin, S., (1997), Optimal Control of the Chemotherapy of HIV, J. Math. Biol., 35, pp.775-792.
[19] Lenhart, S., Workman, J.T., (2007), Optimal Control Applied to Biological Models, Chapman and Hall.
[20] Lenhart, S.M., Yong, J., (1997), Optimal Control for Degenerate Parabolic Equations with Logistic Growth Preprint Institute for Mathematics and Application.
[21] Makinde, O.D., Okosun, K.O., (2011), Impact of chemo-therapy on optimal control of malaria disease with infected immigrants, BioSystems, 104, pp.32-41.
[22] Marco, A.L.C., Takashi, Y., (2001), Optimal and suboptimal control in Dengue epidemics, Optimal control applications and methods, 22, pp.63-73. doi: 10.1002/oca.683
[23] Martcheva, M., Castillo-Chavez, C., (2003), Disease with chronic stage in a population with varying size, Math. Biosci., 182, pp.1-25.
[24] Martin, N.K., Vickerman, P., Foster, G.R., Hutchinson, S.J., Goldberg, D.J., Hickman, M., (2011), Can antiviral therapy for epatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility, Journal of Hepatology, 54, pp.1137-1144.
[25] Martin, N.K., Vickerman, P., Hickman, M., (2011), Mathematical modelling of hepatitis C treatment for injecting drug users, Journal of Theoretical Biology, 274, pp.58-66.
[26] Mtisi, E., Rwezaura, H., Tchuenche, J.M., (2009), A mathematical analysis of malaria and Tuberculosis co-dynamics, Discrete and Continuos Dynamical Systems Series B, 12(4), pp.827-864.
[27] Nakul, C., Hyman, J.M., Cushing, J.M., (2008), Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model, Bulletin of Mathematical Biology, 70, pp.1272-1296.
[28] National AIDS Treatment Advocacy Project, (2005), Hepatitis C virus (HCV) and HCV/HIV co-infection handbook, version V.
[29] Okosun, K.O., Ouifki, R., Marcus, N., (2011), Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity, BioSystems, 106, pp.136-145. doi:10.1016/j.biosystems.2011.07.006
[30] Papaevangclou, V., Pollack, H., Rochford, G., et.al., (1998), Increased transmission of vertical hepatitis C virus (HCV) infection to human immunodeficiency virus (HIV)- infected infants of HIV- and HCV-coinfected women, The Journal of Infectious Disease, 178(4), pp.1047-1052.
[31] Pontryagin, L.S., Boltyanskii, V.G., Gamkrelidze, R.V., Mishchenko, E.F., (1962), The mathematical theory of optimal processes, Wiley, New York.
[32] Qesmi, R., Wu, J., Heffernan, J.M., (2010), Influence of backward bifurcation in a model of hepatitis B and C viruses, Math. Biosc., 224, pp.1180-125.
[33] Rachik, H.M., Saadi, S., Tabit, Y., Yousfi, N., (2009), Optimal control of tuberculosis with exogenous reinfection, Applied Mathematical Sciences, 3(5), pp.231-240.
[34] Roberts, E.A., Yeung, L., (2002), Maternal-infant transmission of hepatitis C virus infection, Hepatology, 36(5B), pp.S106 - S113.
[35] Suresh, P.S., (1978), Optimal Quarantine programmes for controlling an epidemic spread, Journal Opl. Res. Soc. Pergamon press., 29(3), pp.265-268.
[36] Suresh, P.S., (1978), Optimal control of some simple deterministic epidemic models, Journal Operational Research Society, Pergamon Press, 29(2), pp.129-136.
[37] Wickwire, K., (1975), A note on the optimal control of carrier - borne epidemic, Journal of Applied probability, 12, pp.565-568.

[38] Wiemer, C., (1987), Optimal disease control through combined use of preventive and curative measures, Journal of Development Economics, North-Holland, 25, pp.301-319.
[39] Xiefei, Y., Yun, Z., Jianliang, L., (2007), Optimal quarantine and isolation strategies in epidemics control. World Journal of Modelling and Simulation, 3(3), 202 - 211.
[40] Yuan, J., Yang, Z., (2007), Global stability of an SEI model with acute and chronic stages, J. Comput. Appl. Math. doi:10.1016/j.cam.2007.01.042.
[41] Zaman, G., Yong, H. K., Jung, I.H., (2008), Stability analysis and optimal vaccination of an SIR epidemic model, BioSystems 93, pp.240-249.

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