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Control of Diseases Epidemic Spreading through Metapopulation Models

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Abstract: We study a system of ordinary differential equations which describes the metapopulation SIR model. The main target is to control the epidemic spreading using the structure of connections between cities. For this purpose, we formulate optimal control strategy that the control represents a drug treatment and Prevention strategies . Some methods are given in numerical example section such as control through spectral radius of movement matrix or optimal control through travelling between cities. Existence results for the optimal control are studied.

Keywords: Optimal control theory, Epidemiological models, Epidemic spreading

1. INTRODUCTION

Differential and dynamical models is applied to analysis and to make decision in biological models [1, 2]. Optimal control theory is a branch of differential equations that can be used in restraining the spread of infectious diseases. The study by Kirschner *et al.* [3] used optimal control theory to establish the optimal treatment strategy for the managing of antiretroviral drug in individuals who were HIV positive. Geometric optimal control theory is applied to epidemic model in [4]. In that paper, a general SIR-model with vaccination and treatment is considered as an optimal control problem over a fixed time and it is shown that the optimal vaccination schedule can be singular, but that treatment schedules are not. Optimal control techniques is applied to study optimal strategies for restraining the spread of malaria [6]. Fister and Donnelly [7] also used optimal control theory to determine the conditions for the elimination of tumor cells in an individuals under treatment for Cancer.

The structure of a population or group plays an important role in the dynamics of a disease transmission [8, 9, 10]. Epidemiological models are almost multigroup models. Groups can be classified into geographical groups such as cities, countries and communities, behavioral groups like different patterns of contact and high risk groups or epidemiological groups like vertical transmission and co-infection of multiple origins of the disease agent[11].

One of the important models in epidemiology is metapopulation model. Consider a human disease that is spread in a large country with a small number of potentially large cities. Suppose that the movements between cities are fast, and the propagation of an epidemic takes place only at the destination location. In this setting, travel of individuals between cities must play some role in the spreading of the disease. Based on continuous time model, Arino and van den Driessche investigated on role of cities in the epidemic spreading [12]. Arino *et al.* studied a metapopulation malaria model using SI and SIRS models for the vectors and hosts [13]. Multigroup models can also be used to investigate infectious diseases with multiple hosts such as West-Nile virus and vector borne diseases. For a survey of multigroup models, we refer to [11]. For a class of multigroup SIR epidemic models with varying subpopulation sizes, Guo *et al.* established that the global dynamics are completely determined by the basic reproduction number R_0. Basic reproduction number, local analysis and global analysis of Metapopulation SIR model have been presented in [14].

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We develop optimal control formulation of Metapopulation SIR model with three cities. The model and optimal control formulation are introduced in the next section.The basic reproduction ratio will be computed in section 3. We present the existence of optimal control results in section 4. The optimal control is characterized in terms of the adjoints and states by Pontryagin Maximum Principle (PMP) in section 5. The control strategies are considered. Numerical examples for optimal control formulation are presented in section 6. In section 7 the structure of movement matrix and it's impact on epidmemic spreading is investigated and these results are illustrated with numerical examples.

2. THE MODEL

Our metapopulation model is, formulated by dividing the population of size $N(t)$ into three distinct cities. We study the transmission dynamics in cities with an SIR(susceptible-infected-recovered) model. For $k = 1,2,3$; the k-th city is divided into three compartments: the susceptibles, infectious, and recovered, whose numbers of individuals at time t are denoted by $S_k(t); I_k(t)$ and $R_k(t)$; respectively. For $1 \le i; j \le n$; the disease transmission coefficient between compartments S_i and I_j is denoted by $\beta_i j$; so that the new infection occurred in the k-th group is given by $\sum_{j=1}^{3} \beta_{kj} S_k I_j$. The matrix B = (β_{ij}) is the contact matrix, where $\beta_{ij} \ge 0$: Within the k-th group, it is assumed that natural death occurs in S_k, I_k and R_k compartments with rate constants d_k^S, d_k^I and d_k^R respectively. Individuals in I_k have another death due to disease with rate constant ε_k. The inflow of susceptible individuals into the groups is given by a constant Λ_k. Suppose that individuals in I_k recover with a rate constant γ_k; and once recovered they remain immuned for the disease. Based on these assumptions, the following system of differential equations can be expressed (for i = 1, 2, 3):

$$\begin{cases} \dot{S}_i = \Lambda_i - d_i^S S_i - \sum_{j=1}^{3} \beta_{ij} S_i I_j \\ \dot{I}_i = \sum_{j=1}^{3} \beta_{ij} S_i I_j - (d_i^I + \varepsilon_i + \gamma_i) I_i \\ \dot{R}_i = \gamma_i I_i - d_i^R R_i \end{cases} \tag{1}$$

or in other word:

$$\begin{cases} \dot{S}_1 = \Lambda_1 - d_1^S S_1 - \beta_{11} S_1 I_1 - \beta_{12} S_1 I_2 - \beta_{13} S_1 I_3 \\ \dot{I}_1 = \beta_{11} S_1 I_1 + \beta_{12} S_1 I_2 + \beta_{13} S_1 I_3 - (d_1^I + \varepsilon_1 + \gamma_1) I_1 \\ \dot{R}_1 = \gamma_1 I_1 - d_1^R R_1 \\ \dot{S}_2 = \Lambda_2 - d_2^S S_2 - \beta_{21} S_2 I_1 - \beta_{22} S_2 I_2 - \beta_{23} S_2 I_3 \\ \dot{I}_2 = \beta_{21} S_2 I_1 + \beta_{22} S_2 I_2 + \beta_{23} S_2 I_3 - (d_2^I + \varepsilon_2 + \gamma_2) I_2 \\ \dot{R}_2 = \gamma_2 I_2 - d_2^R R_2 \\ \dot{S}_3 = \Lambda_3 - d_3^S S_3 - \beta_{31} S_3 I_1 - \beta_{32} S_3 I_2 - \beta_{33} S_3 I_3 \\ \dot{I}_3 = \beta_{31} S_3 I_1 + \beta_{32} S_3 I_2 + \beta_{33} S_3 I_3 - (d_3^I + \varepsilon_3 + \gamma_3) I_3 \\ \dot{R}_3 = \gamma_3 I_3 - d_3^R R_3 \end{cases} \tag{2}$$

The following parameters appear in our model:

β_{ij} : transmission coefficient between S_i and I_j;

d_k^S, d_k^I, d_k^R : natural death rates of $S; I; R$ in the k-th group, respectively;

Λ_k : inflow of susceptible individuals into the k-th group;

γ_k : recovery rate of infectious individuals in the k-th group;

ε_k : disease-caused death rate in the k-th group.

All parameter values are assumed to be nonnegative and $d_k^S, d_k^I, d_k^R, \Lambda_k > 0$. Using the same parameters and class names as in the model (1), we suggested the following ODEs system (3) describing the model with controls.

$$\begin{cases} \dot{S}_1 = \Lambda_1 - (d_1^S + u_1)S_1 - \beta_{11}S_1I_1 - \beta_{12}S_1I_2(1-v_{12}) - \beta_{13}S_1I_3(1-v_{13}) \\ \dot{I}_1 = \beta_{11}S_1I_1 + \beta_{12}S_1I_2(1-v_{12}) + \beta_{13}S_1I_3(1-v_{13}) - (d_1^I + \varepsilon_1 + \gamma_1 + v_1)I_1 \\ \dot{R}_1 = u_1S_1 + \gamma_1I_1 - d_1^RR_1 + v_1I_1 \\ \dot{S}_2 = \Lambda_2 - (d_2^S + u_2)S_2 - \beta_{21}S_2I_1(1-v_{21}) - \beta_{22}S_2I_2 - \beta_{23}S_2I_3(1-v_{23}) \\ \dot{I}_2 = \beta_{21}S_2I_1(1-v_{21}) + \beta_{22}S_2I_2 + \beta_{23}S_2I_3(1-v_{23}) - (d_2^I + \varepsilon_2 + \gamma_2 + v_2)I_2 \\ \dot{R}_2 = u_2S_2 + \gamma_2I_2 - d_2^RR_2 + v_2I_2 \\ \dot{S}_3 = \Lambda_3 - (d_3^S + u_3)S_3 - \beta_{31}S_3I_1(1-v_{31}) - \beta_{32}S_3I_2(1-v_{32}) - \beta_{33}S_3I_3 \\ \dot{I}_3 = \beta_{31}S_3I_1(1-v_{31}) + \beta_{32}S_3I_2(1-v_{32}) + \beta_{33}S_3I_3 - (d_3^I + \varepsilon_3 + \gamma_3 + v_3)I_3 \\ \dot{R}_3 = u_3S_3 + \gamma_3I_3 - d_3^RR_3 + v_3I_3 \end{cases} \quad (3)$$

The control functions $u_i(t)$, v_i and $v_{ij}(t)$ have to be bounded on [0, 1] and Lebesgue integrable functions. $u_i(t), i = 1,2,3$ measure the time dependent efforts on the preventive strategy (such as vaccination) of susceptible individuals in S_i, to reduce the number of individuals that may be infectious. The control functions v_{ij} measures the time dependent efforts on the limitation strategy of immigration of susceptible individuals from city *i* to *j*. $v_i(t)$ measures the time dependent efforts on the treatment of infected individuals in city *i* to reduce the number of infected individuals. This control will have an impact on the output flow of people from the The objective functional to be minimized is:

$$J(u_1,u_2,u_3,v_1,v_2,v_3,v_{12},v_{13},v_{21},v_{23},v_{31},v_{32}) = \quad (4)$$

$$\int_0^T g(I,U)dt = \int_0^T AI_1^2 + BI_2^2 + CI_3^2 + Du_1^2 + Eu_2^2 + Fu_3^2 + Gv_{12}^2 + Kv_{13}^2$$

$$+ Lv_{21}^2 + Nv_{22}^2 + Ov_{31}^2 + Pv_{32}^2 + Qv_1^2 + Zv_2^2 + Wv_3^2dt.$$

Here, $A, B, C, D, E, F, G, K, L, N, O, P$ are adjustment parameters. They are converting the dimension from population number into cost expended over a finite time period of T years. We seek an optimal control

$$(u_1^*, u_2^*, u_3^*, v_1^*, v_2^*, v_3^*, v_{12}^*, v_{13}^*, v_{21}^*, v_{23}^*, v_{31}^*, v_{32}^*)$$

such that

$$J(u_1^*, u_2^*, u_3^*, v_1^*, v_2^*, v_3^*, v_{12}^*, v_{13}^*, v_{21}^*, v_{23}^*, v_{31}^*, v_{32}^*) =$$

$$\min\{J(U) \mid (u_1, u_2, u_3, v_1, v_2, v_3, v_{12}, v_{13}, v_{21}, v_{23}, v_{31}, v_{32}) \in U\}$$

where

$U = \{(u_1, u_2, u_3, v_1, v_2, v_3, v_{12}, v_{13}, v_{21}, v_{23}, v_{31}, v_{32}) \mid u_i, v_i, v_{ij}\ measerable\}$ and $\{0 \le u_i, v_i, v_{ij} \le 1, \quad t \in [0,T]\}$ is the control set.

3. BASIC REPRODUCTION NUMBER

The global behavior of the metapopulation model depends on the basic reproduction number, i.e., an average number of secondary cases produced by a single infective individual, who is introduced into an entirely susceptible population. System (1) has an infection-free equilibrium in which the susceptible components are positive and the infective components equals to zero. According to definition of R_0, for R_0>1, initial infection will spread, and the disease will disappear if R_0 < 1. Denote this infection-free equilibrium by $E = (S_1^0, 0, 0, S_2^0, 0, 0, S_3^0, 0, 0)$ where $S_i^0 = \dfrac{\Lambda_i}{d_i^S}$. Analyzing the local stability of this point gives the epidemic threshold condition, R_0. E is locally asymptotically stable if R_0 < 1, and unstable if R_0 > 1. Thanks to [14] basic reproductive ratio is given by $R_0 = \rho(M_0)$ where

$$M_0 = \left(\frac{\beta_{ij} S_i^0}{d_i^I + \varepsilon_i + \gamma_i} \right)_{3\times 3}.$$

Here M_0 called movement matrix and ρ denotes the spectral radius of matrix. We investigate the effect of different prevention strategies on the spread of infectious diseases within a population. The majority of existing papers fall into one of two groups. In the first group, prevention strategies are modeled by a constant parameter and the goal is to understand how changing the value of the parameter changes the dynamics of the system. Often the aim is to determine the best parameter value for a given performance measure. In this manner we can compute basic reproductive ratio,

$$R_0 = \rho \left(\frac{\beta_{ij}(1-v_{ij}) S_i^0}{d_i^I + \varepsilon_i + \gamma_i + v_i} \right)_{3\times 3} \tag{5}$$

where $S_i^0 = \dfrac{\Lambda_i}{d_i^S + u_i}$

In the second group, prevention strategies are allowed to vary as a function of time and the goal is to determine the best function for a given performance measure. We will investigate this point of view in the following.

4. DERIVING THE OPTIMAL SOLUTION

In this section, we derive the optimal control system for minimizing the functional 4 subject to 1. In order to derive the necessary conditions for this optimal control, we use Pontryagin's Maximum Principle [18]. The Hamiltonian is defined as follows:

$$
\begin{aligned}
H \quad &= AI_1^2 + BI_2^2 + CI_3^2 + Du_1^2 + Eu_2^2 + Fu_3^2 + \\
&Gv_{12}^2 + Kv_{13}^2 + Lv_{21}^2 + Nv_{23}^2 + Ov_{31}^2 + Pv_{32}^2 + Qv_1^2 + Zv_2^2 + Wv_3^2 + \\
&Y_1(\Lambda_1 - (d_1^S + u_1)S_1 - \beta_{11}S_1I_1 - \beta_{12}S_1I_2(1-v_{12}) - \beta_{13}S_1I_3(1-v_{13})) + \\
&Y_2(\beta_{11}S_1I_1 + \beta_{12}S_1I_2(1-v_{12}) + \beta_{13}S_1I_3(1-v_{13}) - (d_1^I + \varepsilon_1 + \gamma_1 + v_1)I_1) + \\
&Y_3(u_1S_1 + \gamma_1I_1 - d_1^R R_1 + v_1I_1) + \\
&Y_4(\Lambda_2 - (d_2^S + u_2)S_2 - \beta_{21}S_2I_1(1-v_{21}) - \beta_{22}S_2I_2 - \beta_{23}S_2I_3(1-v_{23})) + \\
&Y_5(\beta_{21}S_2I_1(1-v_{21}) + \beta_{22}S_2I_2 + \beta_{23}S_2I_3(1-v_{23}) - (d_2^I + \varepsilon_2 + \gamma_2 + v_2)I_2) + \\
&Y_6(u_2S_2 + \gamma_2I_2 - d_2^R R_2 + v_2I_2) + \\
&Y_7(\Lambda_3 - (d_3^S + u_3)S_3 - \beta_{31}S_3I_1(1-v_{31}) - \beta_{32}S_3I_2(1-v_{32}) - \beta_{33}S_3I_3) + \\
&Y_8(\beta_{31}S_3I_1(1-v_{31}) + \beta_{32}S_3I_2(1-v_{32}) + \beta_{33}S_3I_3 - (d_3^I + \varepsilon_3 + \gamma_3 + v_3)I_3) + \\
&Y_9(u_3S_3 + \gamma_3I_3 - d_3^R R_3 + v_3I_3).
\end{aligned} \tag{6}
$$

Suppose that $(u_1^*, u_2^*, u_3^*, v_1^*, v_2^*, v_3^*, v_{12}^*, v_{13}^*, v_{21}^*, v_{23}^*, v_{31}^*, v_{32}^*)$ is an optimal control with corresponding states $(S_1, I_1, R_1, S_2, I_2, R_2, S_3, I_3, R_3)$. To characterize the optimal control, the Hamiltonian and adjoint equations are constructed.

Theorem 4.1 *There exists an optimal control* $(u_1^*, u_2^*, u_3^*, v_1^*, v_2^*, v_3^*, v_{12}^*, v_{13}^*, v_{21}^*, v_{23}^*, v_{31}^*, v_{32}^*)$ *and corresponding solution* $(S_1^*, I_1^*, R_1^*, S_2^*, I_2^*, R_2^*, S_3^*, I_3^*, R_3^*)$, *that minimizes* J *over* $[0,T]$. *Furthermore, there exists adjoint functions* $(Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9)$ *such that*

$$
\begin{cases}
\dot{Y}_1 = & Y_1(d_1^S + u_1 + \beta_{11}I_1 + \beta_{12}I_2(1-v_{12}) + \beta_{13}I_3(1-v_{13})) \\
& - Y_2(\beta_{11}I_1 + \beta_{12}I_2(1-v_{12}) + \beta_{13}I_3(1-v_{13})) - Y_3u_1 \\
\dot{Y}_2 = & -2AI_1 + Y_1(\beta_{11}S_1) - Y_2(\beta_{11}S_1 - (d_1^I + \varepsilon_1 + \gamma_1 + v_1)) \\
& - Y_3(\gamma_1 + v_1) + Y_4(\beta_{21}S_2(1-v_{21})) - Y_5(\beta_{21}S_2(1-v_{21})) \\
& + Y_7(\beta_{31}S_3(1-v_{31})) - Y_8(\beta_{31}S_3(1-v_{31})) \\
\dot{Y}_3 = & Y_3d_1^R \\
\dot{Y}_4 = & Y_4(d_2^S + u_2 + \beta_{21}I_1(1-v_{21}) + \beta_{22}I_2 + \beta_{23}I_3(1-v_{23})) \\
& - Y_5(\beta_{21}I_1(1-v_{21}) + \beta_{22}I_2 + \beta_{23}I_3(1-v_{23})) - Y_6u_2 \\
\dot{Y}_5 = & -2BI_2 + Y_1(\beta_{12}S_1(1-v_{12})) - Y_2(\beta_{12}S_1(1-v_{12})) \\
& + Y_4(\beta_{22}S_2) - Y_5(\beta_{22}S_2 - (d_2^I + \varepsilon_2 + \gamma_2 + v_2)) - Y_6(\gamma_2 + v_2) \\
& + Y_7(\beta_{32}S_3(1-v_{32})) - Y_8(\beta_{32}S_3(1-v_{32})) \\
\dot{Y}_6 = & Y_6d_2^R \\
\dot{Y}_7 = & Y_7(d_3^S + u_3 + \beta_{31}I_1(1-v_{31}) + \beta_{32}I_2(1-v_{32}) + \beta_{33}I_3) \\
& - Y_8(\beta_{31}I_1(1-v_{31}) + \beta_{32}I_2(1-v_{32}) + \beta_{33}I_3) - Y_9u_3 \\
\dot{Y}_8 = & -2CI_3 + Y_1(\beta_{13}S_1(1-v_{13})) - Y_2(\beta_{13}S_1(1-v_{13})) \\
& + Y_4(\beta_{23}S_2(1-v_{23})) - Y_5(\beta_{23}S_2(1-v_{23})) + Y_7(\beta_{33}S_3) \\
& - Y_8(\beta_{33}S_3 - (d_3^I + \varepsilon_3 + \gamma_3 + v_3)) - Y_9(\gamma_3 + v_3) \\
\dot{Y}_9 = & Y_9d_3^R
\end{cases} \tag{7}
$$

with transversality conditions $Y_i(T) = 0, i = 1,2,3,4$. The following characterization holds

$$\begin{cases} u_1^* = \min\{\max\{\frac{(Y_1 - Y_3)S_1}{2D}, 0\}, 1\} \\ u_2^* = \min\{\max\{\frac{(Y_4 - Y_6)S_2}{2E}, 0\}, 1\} \\ u_3^* = \min\{\max\{\frac{(Y_7 - Y_9)S_3}{2F}, 0\}, 1\} \end{cases} : \begin{cases} v_1^* = \min\{\max\{\frac{(Y_2 - Y_3)I_1}{2Q}, 0\}, 1\} \\ v_2^* = \min\{\max\{\frac{(Y_5 - Y_6)I_2}{2Z}, 0\}, 1\} \\ v_3^* = \min\{\max\{\frac{(Y_8 - Y_9)I_3}{2W}, 0\}, 1\}. \end{cases}$$

and

$$\begin{cases} v_{12}^* = \min\{\max\{\frac{(Y_2 - Y_1)\beta_{12}S_1I_2}{2G}, 0\}, 1\} \\ v_{13}^* = \min\{\max\{\frac{(Y_2 - Y_1)\beta_{13}S_1I_3}{2K}, 0\}, 1\} \\ v_{21}^* = \min\{\max\{\frac{(Y_5 - Y_4)\beta_{21}S_2I_1}{2L}, 0\}, 1\} \\ v_{23}^* = \min\{\max\{\frac{(Y_5 - Y_4)\beta_{23}S_2I_3}{2N}, 0\}, 1\} \\ v_{31}^* = \min\{\max\{\frac{(Y_8 - Y_7)\beta_{31}S_3I_1}{2O}, 0\}, 1\} \\ v_{32}^* = \min\{\max\{\frac{(Y_8 - Y_7)\beta_{32}S_3I_2}{2P}, 0\}, 1\}. \end{cases}$$

Proof. Applying Pontryagin Maximum Principle, we obtain

$$\dot{Y}_1 = -\frac{\partial H}{\partial S_1}, \quad Y_1(T) = 0$$

evaluated at the optimal control and corresponding states, which results in the stated adjoint system (7). Similar progress can be done for $Y_2,...,Y_9$. By considering the optimality conditions for Hamiltonian, $\frac{\partial H}{\partial u_i} = \frac{\partial H}{\partial v_i} = \frac{\partial H}{\partial v_{ij}} = 0$ and solving them, the characterization of optimal control functions can be derived. To illustrate the characterization of u_1^* we have

$$\frac{\partial H}{\partial u_1} = 2Du_1 - (Y_1S_1 - Y_3S_1) = 0 \Rightarrow u_1^* = \frac{(Y_1 - Y_3)S_1}{2D}.$$

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

$$u_1 = \begin{cases} \frac{(Y_1 - Y_3)S_1}{2D} & if \quad 0 \le \frac{(Y_1 - Y_3)S_1}{2D} \le 1, \\ 0 & if \quad \frac{(Y_1 - Y_3)S_1}{2D} < 0, \\ 1 & if \quad \frac{(Y_1 - Y_3)S_1}{2D} > 1. \end{cases}$$

In compact notation, we have $u_1^* = \min\{\max\{\frac{(Y_1 - Y_3)S_1}{2D}, 0\}, 1\}$. The rest of the control functions can be found by a similar method.

5. NUMERICAL RESULTS

In this section, we investigate numerically an optimal policy and prevention strategies of our model. The state and adjoint system of differential equations together with the control characterization above form the optimal control system to be solved numerically. As we know the state equations have initial conditions, while the adjoint equations have final time condition and we cannot solve the optimality system directly by sweeping forward in time method. Thus forward-backward sweep method (thanks to Lenhart and Workman[2]), is used. For the control function, an initial estimate is made. Then the state system is solved forward in time from the dynamics using a Runge Kutta method of the fourth order(RK4). Results for state values are placed in the right-hand sides of the adjoint differential equations. Then the adjoint system is solved backward in time with given final conditions, again employing a RK4 method. Both state and adjoint values are used to update the control using the characterization, and then the process is repeated. This iterative process terminates when current state, adjoint, and control values converge sufficiently.

5.1. Example(1): Minimum cost static control

Now we will use the MATLAB program to ascertain how each control parameter affects the solution. This example illustrates how constant parameter control could change the future of epidemic spreading. Let us enter the following values in the model system (1):

Parameters and values			
$\beta_{ij} = 1/30$	$1 \le i, j \le 3$	$A = B = 1$	$u_1 = 0.1$
$d_1^S = 1/10$	$d_1^I = 1/10$	$C = D = 1$	$u_2 = 0.1$
$d_2^S = 1/10$	$d_2^I = 1/10$	$E = F = 1$	$u_3 = 0.1$
$d_3^S = 1/10$	$d_3^I = 1/10$	$G = K = 1$	$v_1 = 0$
$d_1^R = 1/10$	$\varepsilon_1 = 1/3$	$L = O = 1$	$v_2 = 0$
$d_2^R = 1/10$	$\varepsilon_2 = 1/3$	$P = Q = 1$	$v_3 = 0$
$d_3^R = 1/10$	$\varepsilon_3 = 1/3$	$W = Z = 1$	$T = 1000$
$S_1(0) = 0.95$	$I_1(0) = 0.05$	$R_1(0) = 0$	
$S_2(0) = 1.4$	$I_2(0) = 0.1$	$R_2(0) = 0$	
$S_3(0) = 1.2$	$I_3(0) = 0.8$	$R_3(0) = 0$	
$\gamma_1 = 1/2$	$\Lambda_1 = 1$	$v_{12} = v_{13} = 0$	
$\gamma_2 = 1/2$	$\Lambda_2 = 3/2$	$v_{21} = v_{23} = 0$	
$\gamma_3 = 1/2$	$\Lambda_3 = 2$	$v_{31} = v_{32} = 0$	

According to (3) the reproduction number for this example equals to $R_0 = 1.6071$ and there exists an asymptotically stable endemic equilibrium point

$$(6.2222, 0.4048, 2.0238, 9.3333, 0.6071, 3.0357, 12.4444, 0.8095, 4.0476)$$

that system tends to this point. By using constant parameter control $u_1 = u_2 = u_3 = 0.1, v_1 = v_2 = v_3 = 0, v_{12} = v_{13} = v_{21} = v_{23} = v_{31} = v_{22} = 0$ one can compute the basic

reproductive number by (5) and obtain $R_0 = .8036$ The system tends to disease-free equilibrium point $(5,0,5,7.5,0,7.5,10,0,10)$ and outbreak does not occur. Here the objective functional

$$J = \int_0^T AI_1^2 + BI_2^2 + CI_3^2 + Du_1^2 + Eu_2^2 + Fu_3^2 + Gv_{12}^2 + Kv_{13}^2 + Lv_{21}^2 + Nv_{23}^2$$

$$+ Ov_{31}^2 + Pv_{32}^2 + Qv_1^2 + Wv_2^2 + Zv_3^2 dt$$

will reduce to $J = \int_0^T AI_1^2 + BI_2^2 + CI_3^2 dt$ if no control is used and in constant parameter control will reduce to

$$J(u_1, u_2, u_3) = \int_0^T AI_1^2 + BI_2^2 + CI_3^2 + Du_1^2 + Eu_2^2 + Fu_3^2 dt.$$

The final cost is $J = 1175.8$ when we have no control on processes and $J = 30.6442$ for constant parameter control strategy. Despite the control of outbreak, it seems that the cost increases greatly. One can solve the simple optimization problem to find the best $(u1, u_2, u_3, v_1, ..., v_{31}, v_{32})$. This gives

Minimum static controls		
u1 = 0.044	u2 = 0.056	u3 = 0.066
v1 = 0.006	v2 = 0.009	v3 = 0.012
v12 = 0.002	v13 = 0.002	v21 = 0.002
v23 = 0.003	v31 = 0.002	v32 = 0.003

and J = 10.5903. Figure(1) shows the minimum cost static controls.

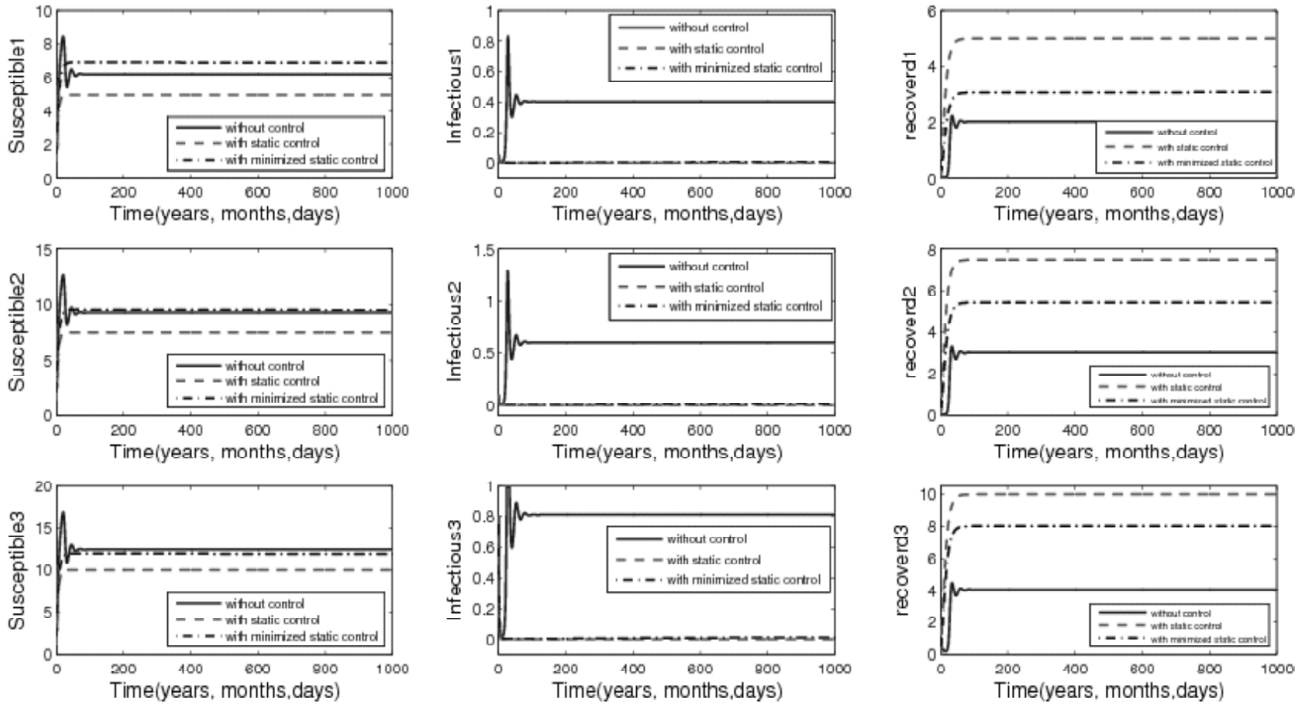

Figure 1: Minimum cost static controls and its effect on epidemic spreading

5.2. Example(2): Optimal control policy

Here, we consider the previous example with optimal control approach that control functions u_i, v_i, v_{ij} can be continuous functions with respect to the time. Let us enter the following values as an adjustment parameters in optimal control method in the previous example:

$$A = B = C = D = E = F = G = K = L = O = P = Q = W = Z = 1, \quad T = 1000$$

As we observe, the model system tends to endemic equilibrium. Figures (2) and (3) shows an optimal schedule and related control functions

$$(u_1, u_2, u_3, v_{12}, v_{13}, v_{21}, v_{23}, v_{31}, v_{32}, v_1, v_2, v_3)$$

for T = 1000. Final cost for optimal control is J = 4.4627 and the final cost without control strategy is J_2 = 1175.8. The optimal control strategy tries to hold costs in a practical level and it depends on our adjusting objective functional J and coefficients A, B, C,

6. TRAVELLING BETWEEN CITIES AND ITS EFFECT ON THE EPIDEMIC SPREADING

In this section we try to depict the impact of movement matrix on the epidemic spreading in the metapopulation model. In the second section the basic reproduction number was computed by spectral radius of movement matrix. The spectral radius of movement matrix changes by removing edges. The decrease of the spectral radius, an important characterizer of metapopulation dynamics, by removing edges is investigated in [21]. In that paper, the minimization of the spectral radius by removing m edges is shown to be an NP-complete problem, which suggests considering heuristic strategies. Several greedy strategies are compared, and several bounds on the decrease of the spectral radius are derived. Here we face the small scale and we can study the minimization of the spectral radius (consequently minimization of the basic reproduction number) by simple computing. Next examples show these.

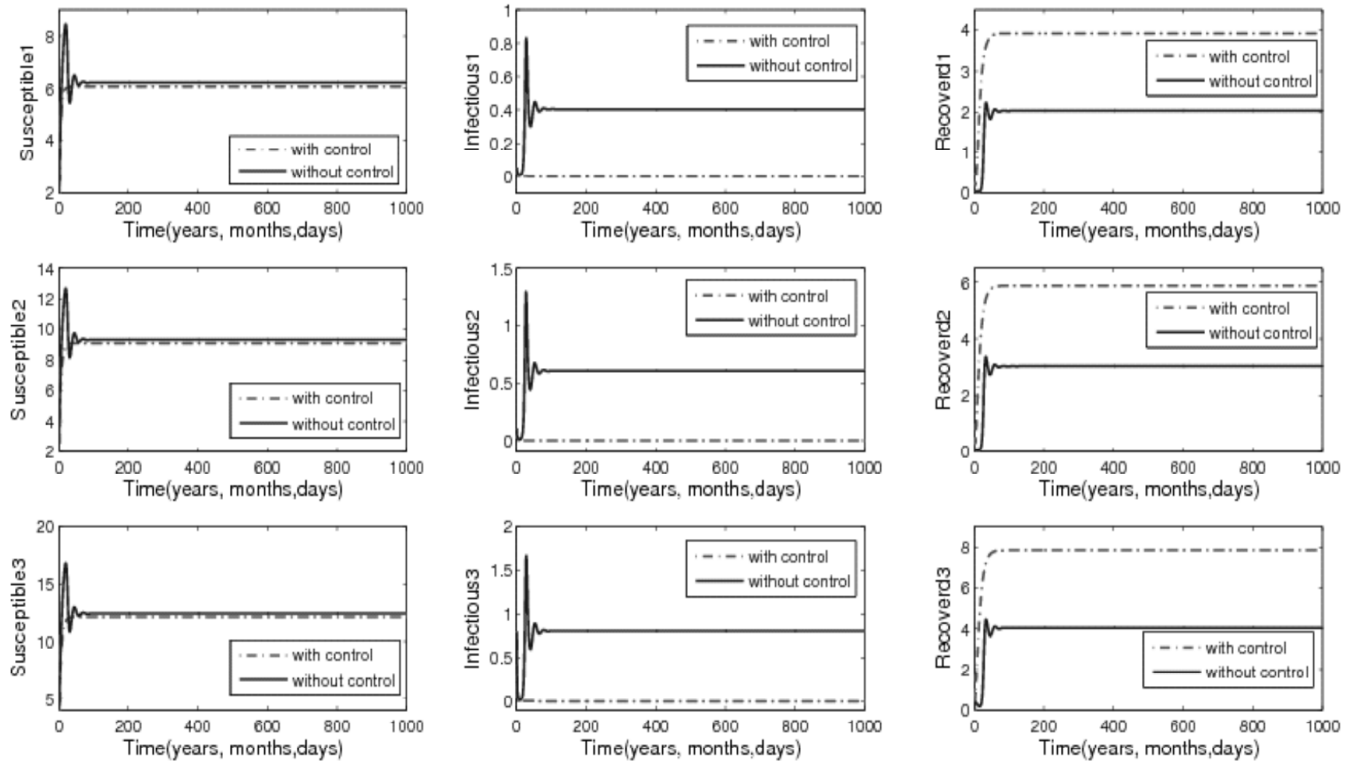

Figure 2: Optimal control strategy. obviously optimal control causes the model system not to tend to endemic equilibrium point and this process occurs with the minimum cost

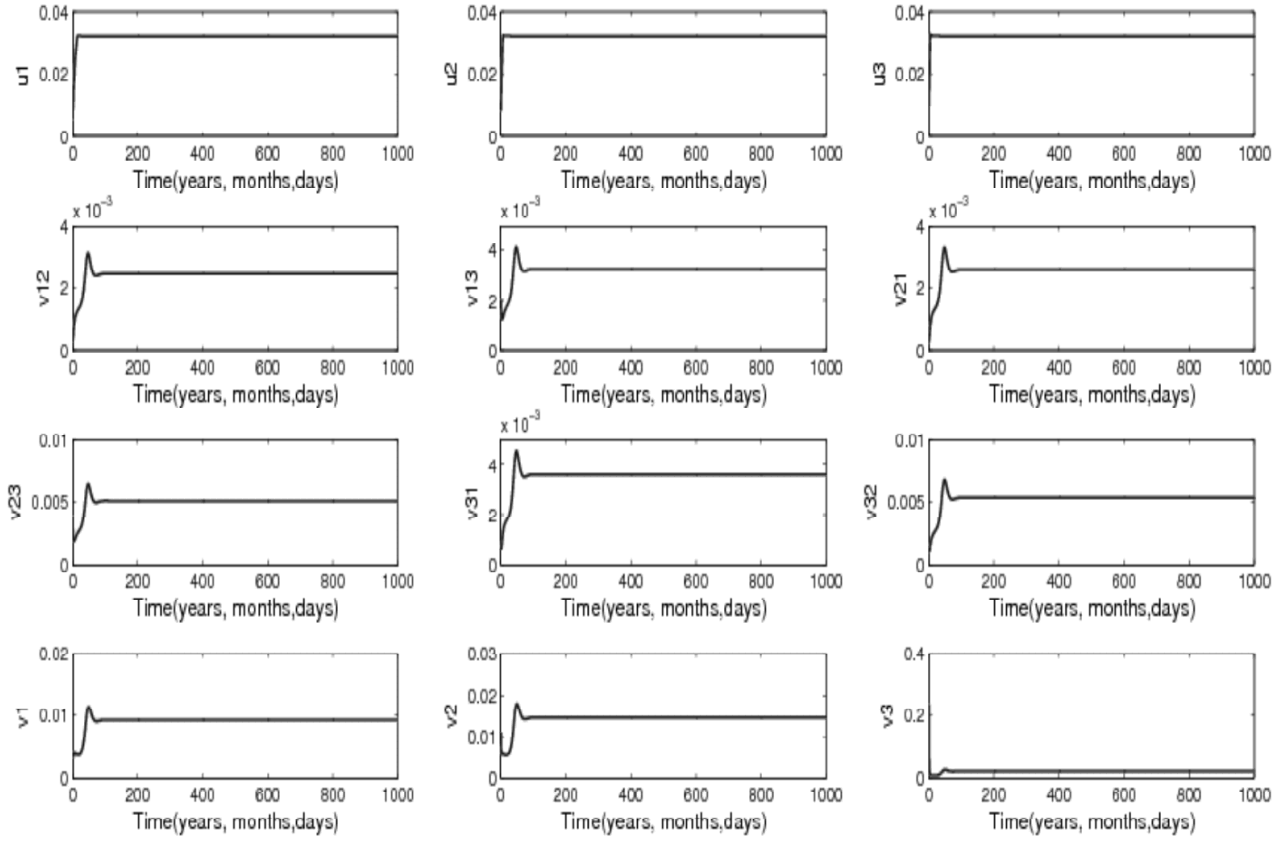

Figure 3: Control function. These functions show control strategy at each moment

6.1. Example(1): Control through spectral radius of movement matrix

Consider the second example in the numerical results section again. The basic reproduction number was $R_0 = 1.6071$. By eliminating e_{ij} edge, v_{ij} value will be changed to 1 in the model. This means that the ij entry of movement matrix reduces to zero and consequently the spectral radius of movement matrix (or the basic reproduction number of model) decreases. The next figure and table show the connection graph of cities and removed edges and their effect on the basic reproduction number. It resembles that this model can be applied to the real models.

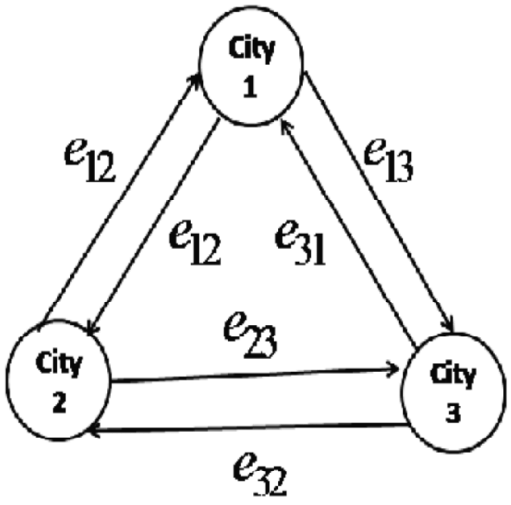

Figure 4: Movement graph

Removed edge	R_0	*Removed edge*	R_0
e_{12}	1.4777	e_{12}, e_{21}	1.4009
e_{13}	1.4286	e_{13}, e_{31}	1.3409
e_{21}	1.4777	e_{23}, e_{32}	1.1884
e_{23}	1.3165	e_{12}, e_{23}	1.2311
e_{31}	1.4286	e_{13}, e_{23}	0.8929
e_{32}	1.3165	e_{12}, e_{13}	1.2500

By removing e_{13} and e_{23} (this means that we exert limitation on trips from city 1 to city 2 and from city 2 to city 3) the basic reproduction number decreases to less than one and consequently the epidemic spreading does not occur. Another practical way to decrease the basic reproduction number is to reduce the rate of the trips. For instance, when epidemic spreading begins, we exert limitation on the trips that leads to reduce the rate of trips reduce to 1/3. Then in the above example the basic reproduction number reduced to $R_0 = 0.9344$.

6.2. Example(2): Optimal control through travelling between cities

Consider the second example in numerical results section again with optimal control approach that control functions v_{ij} can be continuous functions with respect to the time. The optimal strategy is shown in figures below.

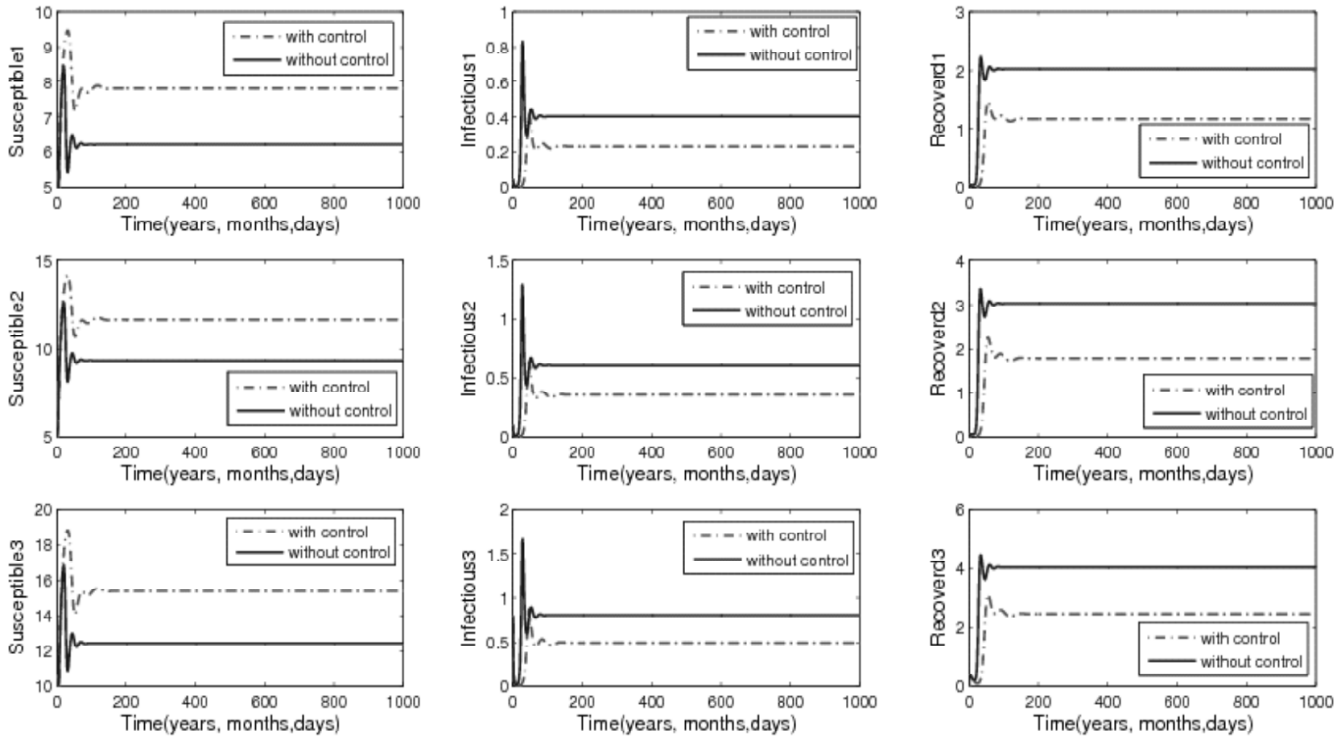

Figure 5: Optimal control on metapopulation model. Here we only use v_{ij}, the limitation strategy of immigration of susceptible individuals from city *i* to *j*, as a control function

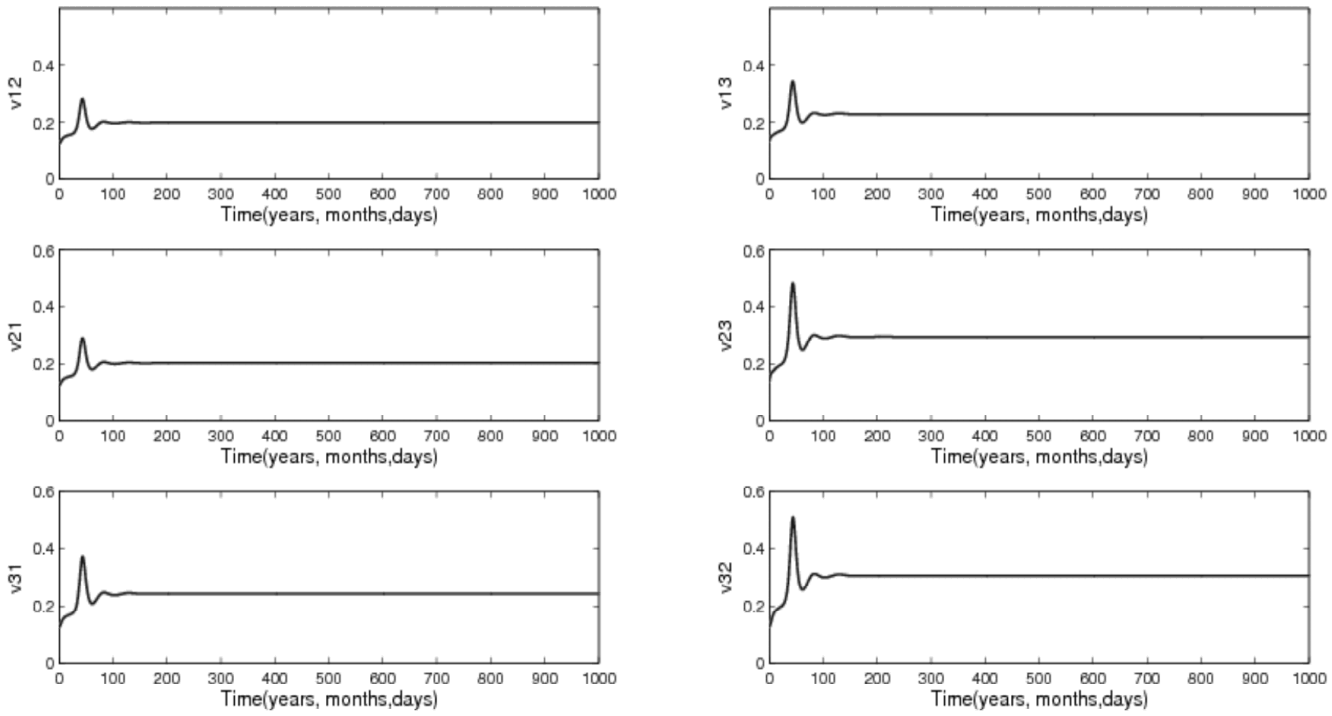

Figure 6: Control functions in movment control model

As we observe, optimal control in this example persists on v_{21} and v_{32}. This is agree with the results on previous example. Note that by adjusting the parameter, we will find more appropriate results.

7. CONCLUSION

This paper has presented mathematical and epidemiological results about the control of disease spreading in metapopulation model. This was designed to examine the following questions:

- How do the structure of movement matrix can affect the dynamics of disease spreading?
- Which conditions on the rate of control parameter can ensure the eradication of disease, or at least minimize its incidence?
- What is the mathematical and numerical consequence of considering such model?
- What is the optimal treatment and prevention strategy?

A deterministic mathematical model for the transmission dynamics of disease in metapopulation model has been built to answer these questions. An important result of this analysis is that the cost-effective balance of prevention and treatment methods can control a disease outbreak. Strategies of optimal control can affect the reducing of death toll and severity of an outbreak. Optimal control theory in our model is a starting point for more elaborate models.

8. ACKNOWLEDGEMENT

It is a pleasure to acknowledge the helpful suggestions made by Dr rooin during the preparation of this paper.

9. APPENDIX

9.1. Existence of an optimal control

The existence of the optimal control can be proved by using a theorem and it's corollary by Fleming and Rishel ([15], Th. 4.1, p. 68-69).

Theorem 8.1: *Consider the control problem with system equations (1), There exists* $(u_1^*, u_2^*, u_3^*, u_4^*) \in U$ *such that* $J(u_1^*, u_2^*, u_3^*, u_4^*) = \min\{J(u_1, u_2, u_3, u_4) \mid (u_1, u_2, u_3, u_4) \in U\}$.

Proof. Let

$$X = \begin{pmatrix} S_1 \\ I_1 \\ R_1 \\ S_2 \\ I_2 \\ R_2 \\ S_3 \\ I_3 \\ R_3 \end{pmatrix} \quad U = \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ v_1 \\ v_2 \\ v_3 \\ v_{12} \\ v_{13} \\ v_{21} \\ v_{23} \\ v_{31} \\ v_{32} \end{pmatrix}.$$

and $f(t, X, U)$ the right hand sight of the (3). So

$f(t, X, U) =$

$$\begin{pmatrix} \Lambda_1 - (d_1^S + u_1)S_1 - \beta_{11}S_1I_1 - \beta_{12}S_1I_2(1-v_{12}) - \beta_{13}S_1I_3(1-v_{13}) \\ \beta_{11}S_1I_1 + \beta_{12}S_1I_2(1-v_{12}) + \beta_{13}S_1I_3(1-v_{13}) - (d_1^I + \varepsilon_1 + \gamma_1 + v_1)I_1 \\ u_1S_1 + \gamma_1I_1 - d_1^R R_1 + v_1I_1 \\ \Lambda_2 - (d_2^S + u_2)S_2 - \beta_{21}S_2I_1(1-v_{21}) - \beta_{22}S_2I_2 - \beta_{23}S_2I_3(1-v_{23}) \\ \beta_{21}S_2I_1(1-v_{21}) + \beta_{22}S_2I_2 + \beta_{23}S_2I_3(1-v_{23}) - (d_2^I + \varepsilon_2 + \gamma_2 + v_2)I_2 \\ u_2S_2 + \gamma_2I_2 - d_2^R R_2 + v_2I_2 \\ \Lambda_3 - (d_3^S + u_3)S_3 - \beta_{31}S_3I_1(1-v_{31}) - \beta_{32}S_3I_2(1-v_{32}) - \beta_{33}S_3I_3 \\ \beta_{31}S_3I_1(1-v_{31}) + \beta_{32}S_3I_2(1-v_{32}) + \beta_{33}S_3I_3 - (d_3^I + \varepsilon_3 + \gamma_3 + v_3)I_3 \\ u_3S_3 + \gamma_3I_3 - d_3^R R_3 + v_3I_3 \end{pmatrix}$$

To use an existence results, we must check the following conditions:

1. f is class C^1 and there exist constant C such that
   - $|f(t,0,0)|<C$
   - $|f_X(t,X,U)|\leq C(1+|U|)$
   - $|f_U(t,X,U)|\leq C$
2. Let $\mathcal{F}$ be the class of feasible pairs (X, U). The set $\mathcal{F}$ with corresponding control in admissible control set is non-empty.
3. $f(t,X,U)=a(t,X)+b(t,X)U$
4. The control set is closed, compact and convex.
5. The integrand of the objective functional is convex in control set. The boundedness of solutions of the system (1) for the finite time interval is used to prove the existence of an optimal control pair. For this, let

$N(t)=S_1(t)+I_1(t)+R_1(t)+S_2(t)+I_2(t)+R_2(t)+S_3(t)+I_3(t)+R_3(t)$ and

$$\frac{dN}{dt}=\Lambda_1+\Lambda_2+\Lambda_3-\sum_{i=1}^{3}(d_i^S S_i+(d_i^I+\varepsilon_i)I_1+d_i^R R_i)\leq \Lambda_1+\Lambda_2+\Lambda_3$$

that shows the boundedness of S_i, I_i, R_i for $i=1,2,3$.

Let check these conditions. Obviously f is C^1 and $|f(t,0,0)|=0<C$. It is easy to check that the entries of $f(t,0,0), f_X(t,X,U)$ and $f_U(t,X,U)$ are in terms of S_i, I_i, R_i for $i=1,2,3$ and some constant parameters. From the boundedness of S_i, I_i, R_i for $i=1,2,3$, the $|f(t,0,0)|, |f_X(t,X,U)|$ and $|f_U(t,X,U)|$ are bounded and we conclude that there exist a constant C such that $|f(t,0,0)|<C, |f_X(t,X,U)|\leq C(1+|U|)$ and $|f_U(t,X,U)|\leq C$ which completes the condition 1. To verify the condition 2, we refer to theorem 2.7 (page37) [16] which is due to E. Picard and E. Lindelof. With the bounds above, it follows that the partial derivative of the state system is bounded which implies the state system is lipschitz continuous with respect to state variables. We may now establish the condition 2 through the Picard-Lindelof theorem. For condition 3, we have

$$a(t,X)=\begin{pmatrix}
\Lambda_1-d_1^S S_1-\beta_{11}S_1I_1-\beta_{12}S_1I_2-\beta_{13}S_1I_3\\
\beta_{11}S_1I_1+\beta_{12}S_1I_2+\beta_{13}S_1I_3-(d_1^I+\varepsilon_1+\gamma_1)I_1\\
\gamma_1 I_1-d_1^R R_1\\
\Lambda_2-d_2^S S_2-\beta_{21}S_2I_1-\beta_{22}S_2I_2-\beta_{23}S_2I_3\\
\beta_{21}S_2I_1+\beta_{22}S_2I_2+\beta_{23}S_2I_3-(d_2^I+\varepsilon_2+\gamma_2)I_2\\
\gamma_2 I_2-d_2^R R_2\\
\Lambda_3-d_3^S S_3-\beta_{31}S_3I_1-\beta_{32}S_3I_2-\beta_{33}S_3I_3\\
\beta_{31}S_3I_1+\beta_{32}S_3I_2+\beta_{33}S_3I_3-(d_3^I+\varepsilon_3+\gamma_3)I_3\\
\gamma_3 I_3-d_3^R R_3+\nu_3 I_3
\end{pmatrix}$$

and $b(t,X)=$

$$\begin{pmatrix} -S_1 & 0 & 0 & 0 & 0 & 0 & \beta_{12}S_1I_2 & \beta_{13}S_1I_3 & 0 & 0 \\ 0 & 0 & & & & & & & & \\ 0 & 0 & 0 & -I_1 & 0 & 0 & -\beta_{12}S_1I_2 & -\beta_{13}S_1I_3 & 0 & 0 \\ 0 & 0 & & & & & & & & \\ S_1 & 0 & 0 & I_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & & & & & & & & \\ 0 & -S_2 & 0 & 0 & 0 & 0 & 0 & 0 & \beta_{21}S_2I_1 & \beta_{22}S_2I_2 \\ 0 & 0 & & & & & & & & \\ 0 & 0 & 0 & 0 & -I_2 & 0 & 0 & 0 & -\beta_{21}S_2I_1 & -\beta_{22}S_2I_2 \\ 0 & 0 & & & & & & & & \\ 0 & S_2 & 0 & 0 & I_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & & & & & & & & \\ 0 & 0 & -S_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_{31}S_3I_1 & \beta_{32}S_3I_2 & & & & & & & & \\ 0 & 0 & 0 & 0 & 0 & -I_3 & 0 & 0 & 0 & 0 \\ -\beta_{31}S_3I_1 & -\beta_{32}S_3I_2 & & & & & & & & \\ 0 & 0 & S_3 & 0 & 0 & I_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & & & & & & & & \end{pmatrix}$$

The control set is $[0, 1]^{12}$ which is closed, compact and convex that is verified the condition 4. Finally to verify the condition 5, it is clear that the integrand of the objective functional is convex on control set and

$$g(t, X, U) = AI_1^2 + BI_2^2 + CI_3^2 + Du_1^2 + Eu_2^2 + Fu_3^2 + Gv_{12}^2 + Kv_{13}^2 + Lv_{21}^2 + Nv_{23}^2$$

$$+ Lv_{21}^2 + Nv_{22}^2 + Ov_{31}^2 + Pv_{32}^2 + Qv_1^2 + Zv_2^2 + Wv_3^2 \geq$$

$$Du_1^2 + Eu_2^2 + Fu_3^2 + Gv_{12}^2 + Kv_{13}^2 + Lv_{21}^2 + Nv_{23}^2 + +Lv_{21}^2 + Nv_{22}^2 + Ov_{31}^2 + Pv_{32}^2 + Qv_1^2 + Zv_2^2 + Wv_3^2 \geq$$

$$\min(D,E,F,G,K,L,M,N,O,P,Q,W)(u_1^2 + u_2^2 + u_3^2 + v_{12}^2 + v_{13}^2 + v_{21}^2 + v_{23}^2 + v_{21}^2 + v_{22}^2 + v_{31}^2 + v_{32}^2 + v_1^2 + v_2^2 + v_3^2)$$

which completes the proof.

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