2013 European Control Conference (ECC)
July 17-19, 2013, Zürich, Switzerland.

Optimal Control of Influenza Epidemic Model with Virus Mutations

Gubar Elena [1] and Quanyan Zhu [2]

Abstract— **Strains of influenza viruses spread in human populations during every season of epidemics. As the infected population size increases, the virus can mutate itself and grow in its strength. The traditional epidemic Susceptible-Infectious-Recovered model does not capture the mutations of viruses, and hence the model is not sufficient to study epidemics where the virus mutate at the same timescale as the epidemic process. In this work, we establish a novel framework to study the epidemic process with mutations of influenza viruses, which couples the Susceptible-Infectious-Recovered model with replicator dynamics used to describe virus mutations. We formulate an optimal control problem to study the optimal strategies for medical treatment and quarantine. We obtain structural results for the optimal strategies and use numerical examples to illustrate our results.**

I. Introduction

The main purpose of this work is to analyze the evolutionary model of the influenza epidemic in urban population, focusing on Susceptible-Infectious-Recovered (SIR) models under the influence of virus mutation. Total urban population is divided into susceptible, infected and recovered subpopulations. Over the time, individuals from these subpopulations randomly interact with each other and change their state. We consider epidemic process as a dynamic process of changing states from susceptible individuals to the infected and finally to the recovered. The influenza epidemic is a fast spreading process, involving the large part of total population. Hence one of the most important topics for research is on the protection of population during annual epidemic season. There exist methods of the preventions that reduce sickness rate to protect population, and medical measures (pharmacological products, quarantine policies, etc.) that reduce the number of the infected in the population.

Another aspect of the influenza epidemic is that different strains of influenza viruses can spread in the population during each epidemic season. Thus, in this work, we focus on evolutionary dynamics to describe the mutation within the virus population. We assume that the virus has two types with different strains and fitness functions. Here the term fitness may be taken to mean the number of offsprings or new copies of viruses. Both types of viruses spread in urban population, and hence during the epidemic process, different parts of population will be infected. In our model, we split infected subpopulations into two subgroup and consider a modified SIR model. Therefore, the epidemic process in urban population depends on the changes in virus population.

In our work, we formulate the Susceptible-Infectious-Recovered (SIR) model under the mechanism of virus mutation that influence on the human population and consider minimization of treatment costs and number of infected in both subpopulations to reduce the speed of epidemics. This complex problem is formulated as an optimal control problem, and the virus mutation is described by replicator dynamics.

The paper is organized as follows. In Section II presents the evolutionary model of viruses. In Section III, we establish the epidemic model for the urban population. Section IV uses Pontryagin's maximum principle find the optimal control and in Section V, we present structural results of the optimal control problem. In Section VI, we use numerical simulation to illustrate our results. The paper is concluded in Section VII.

II. Evolutionary model of virus mutation

Infection disease such as influenza is an urgent health issue in modern urban environment. Influenza spreads faster, especially in large urban populations and influences the lifestyle and working facilities of people. Epidemics depend many factors such as human population's size, virus strain and virulence and it has become important to use effective tools to reduce influence of annual epidemics on human population. Mathematical model of spread of a virus through a population can be used to study those factors that influence the epidemic growth for improving existed treatment and evaluating new effective prevention measures and treatment. In previous research, it has been shown that during epidemic season, influenza virus can mutate, and during the epidemic season, several types of influenza virus circulate in human population. Different mutations of the influenza virus affect human beings with different intensities, and the epidemics evolve depending on the virus type and its intensity. Hence evolution of virus mutation should be taken into account when SIR model is used to model influenza epidemics.

In this work, we couple together two dynamic processes, i.e., the evolution of virus mutation and the epidemic process in human population as one dynamical system. The corresponding scheme of the system is illustrated in Figure 1. At the first level, two different types of influenza virus compete to infect the host for continuing their life cycles, and thereby leading to the spreading of epidemics in urban population. The total population will contain several infected subpopulations, which correspond to different virus types. On the second level, the human population is divided into

[1]St. Petersburg State University, Faculty of Applied Mathematics and Control Processes, Universitetskii prospekt 35, Petergof, Saint-Petersburg, Russia, 198504. alyona.gubar@gmail.com

[2]Coordinated Science Laboratory, Electrical and Computer Engineering, University of Illinois at Urbana Champaign, 1308 W. Main Street, Urbana, IL, USA. zhu31@illinois.edu

subpopulations: susceptible (S), infected (I) and recovered (R) and using different medical tools attempts to reduce number of infected individuals. Spreading of the viruses can be controlled with help of prevention measures, such as medical treatment or isolation of infected individuals of population. Thus, on the second level, we consider SIR model with those control parameters.

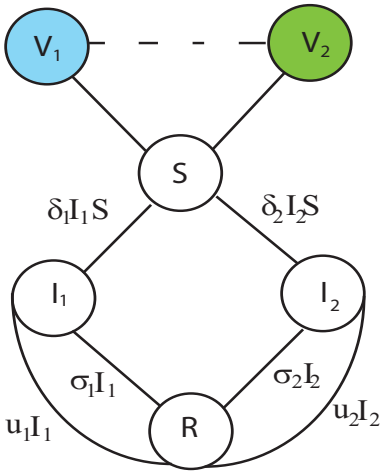

Fig. 1. Transition rule: This scheme describes the reaction of human population to the virus mutation. We assume that the epidemic process can be controlled using treatment or quarantine methods. These measures can de considered as control parameters in the system, and reduce the number of infected human in population and terminate the epidemic process.

At the first level of coupled dynamical system, we use evolutionary dynamics to describe the mutations within the virus population. We first describe the interactions between two virus types using an evolutionary game model, for which we define pure strategies, fitness and rule of changes in population. In the game, two types of viruses enter the competition for human organism as a host, and depending on the strength of the virus, one type can survive or vanish from the virus population.

We assume that the virus has two types or two strains denoted by V_1 and V_2, and without loss of generality, we assume V_1 is a stronger virus than V_2. The fitness of the virus type V_i in the population is $J_i(V_i, V_j), i, j = 1, 2$, which depends on the survival of virus among its infected population (e.g. human beings). Virus life cycle requires a host organism but an occupation of such organism leads to energy costs. Hence the virus payoff J_i is composed of two parts: one is the utility of occupation of host organism, and the other is the cost, i.e. energy costs, $J_i = b_i - C_i$, $b_i > 0$, $C_i > 0$, $b_i < C_i$, $C_1 < C_2$. Utility of occupation b_i is dependent on the population state I_i and hence the mixed strategies $x_1, x_2 \in [0, 1]$ over the set (V_1, V_2) are also dependent on the population states. Here, mixed strategy is defined as fraction of corresponding virus' types circulating in population, and $x_1 + x_2 = 1$.

Depending on the virus strength, the number of people infected by different virus types will be different. We need two epidemic processes to describe the population. We use I_1 to denote the population state for the population infected by type 1 virus, and I_2 is the population state for the population infected by type 2 virus. Both viruses spread over the entire human population, and the interactions between two viruses when attacking the same human organism are described with the following four scenarios:

- if a virus V_1 meets another virus V_1, then payoffs for both are equal to $\frac{b_1 - C_1}{2}$. The virus incurs energy costs C_1 with probability $1/2$ if he can not occupy an organism, and achieve a utility of b_1 with probability $1/2$ if it succeeds in occupation.
- if a virus V_1 meets a virus V_2, then virus V_1 gets b_1 and V_2 gets 0.
- if a virus V_2 meets a virus V_1, then we have the same payoff as above.
- if a virus V_2 meets a V_2, then for both viruses, they obtain payoff of $\frac{b_2 - C_2}{2}$.

The above four cases of competition between the two types of viruses are summarized in the following matrix representation

	V_1	V_2
V_1	$(\frac{b_1-C_1}{2}, \frac{b_1-C_1}{2})$	$(b_1, 0)$
V_2	$(0, b_1)$	$(\frac{b_2-C_2}{2}, \frac{b_2-C_2}{2})$

According to evolutionary game theory, we compare payoff on i-th pure strategy with average payoff of total population. If the difference is positive, then number of individuals using this pure strategy will increase, or decrease otherwise. The average payoff of population is defined as $u(x, x) = \sum_{i=1}^{k} x_i u(e^i, x)$, here e^i is i-th pure strategy, $i = V_1, V_2$, u is a continuous function. Payoff on the i-th pure strategy is defined by $u(e^i, x) = e^1 Ax$, where A is payoff matrix of current symmetric game, $x_i(t)$ are subpopulation of virus V_i, $x_1(t) + x_2(t) = 1$ for all t [17].

We use replicator dynamics [16] to describe the evolution of the mutation process in virus population.

$$\dot{x}_i = \varepsilon[u(e^i, x) - u(x, x)]x_i, \tag{1}$$

where we denote as ε the speed of dynamic (scale factor), as far as mutation process in virus population and epidemic process in human population may develop with different speed, for example virus can mutate faster than spreads in human population.

Solution of system of differential equation 1 may aspire to the stationary state which is symmetric Nash equilibrium. Therefore depends on the parameters b_i, C_i game has two asymmetric Nash equilibriums (V_1, V_2), (V_2, V_1) and one symmetric $(\overline{x}, \overline{x})$, where $\overline{x} = (\overline{x}_1, \overline{x}_2)$, $\overline{x}_1 = \frac{a_2}{a_1 + a_2}, \overline{x}_2 = \frac{a_1}{a_1 + a_2}$, here $a_1 = \frac{b_1 - C_1}{2}$, $a_2 = \frac{b_2 - C_2}{2} - b_2$. Symmetric case is more interesting since both virus' modification influence on the human population.

III. Epidemic process in total urban population

Consider a total urban population of size N and during epidemic season two types of virus circulate in the popu-

lation. Human population is divided into four groups: the susceptible, the infected by virus V_1, the infected by virus V_2, and the recovered. *Susceptible* is a group of human being that are not infected by viruses but can be infected by one or both types of virus, and they do not have immunity to the viruses. We assume that in human population two types of viruses coexist at the same time. Human organisms can be occupied by both types of viruses, hence this leads to competitions between viruses for the host. Depending on the virus strength, we observe that number of people infected by virus i or by virus j can be different, and people that are infected by virus V_1 or V_2 belong to subgroup *Infected*. Recovered subgroup consists of people that are recovered from being infected. The mixing of urban populations allows viruses to spread quickly, and each human in population is assumed to be in contact with others with equal probabilities. Hence when an infected individual interacts with a susceptible one, the virus spread is then made possible. Virus with higher virulence, by our assumption, which is has higher probability of success in spreading when a meeting between the infected and the susceptible occurs.

We model virus spread in urban population using epidemiological SIR model, where a system of differential equations is used to describe the fraction of urban population as a function of time. Then, at time t, n_s, n_{I_1}, n_{I_2}, n_R correspond to fractions of the population who are *Susceptible, Infected* by virus v_1, *Infected* by virus v_2 and *Recovered*, respectively, and for all t, condition $N = n_s + n_{I_1} + n_{I_2} + n_R$ is justified. Define $S(t) = \frac{n_S}{N}, I_1(t) = \frac{n_{I_1}}{N}, I_2(t) = \frac{n_{I_2}}{N}, R(t) = \frac{n_R}{N}(R(t) = 1 - S(t) - I_1(t) - I_2(t))$ as shares of *Susceptible*, *Infected* and *Recovered*. At the beginning of epidemic process $t = 0$, most of people in the population belong to sub-population Susceptible, small group in total population is infected and other people are in recovered sub-population. Hence initial states are: $0 < S(0) = S^0 < 1$, $0 < I_1(0) = I_1^0 < 1$, $0 < I_2(0) = I_2^0 < 1$, $R(0) = 1 - S^0 - I_1^0 - I_2^0$.

We have extended the simple SIR model introduced by [8] to describe the situation with two virus types:

$$\begin{array}{l} \frac{dS}{dt} = -\delta_1 S I_1 - \delta_2 S I_2; \\ \frac{dI_1}{dt} = (\delta_1 S - \sigma_1 - u_1) I_1; \\ \frac{dI_2}{dt} = (\delta_2 S - \sigma_2 - u_2) I_2; \\ \frac{dR}{dt} = (\sigma_1 + u_1) I_1 + (\sigma_2 + u_2) I_2; \end{array} \tag{2}$$

where δ_i are infection rates for virus V_i, $i = 1, 2$, σ_i are recovered rates. Infection rate is defined as a product of the contact rate l and transmissibility of infection, i.e., probability of transmission infection during the contact, δ_{i_0}

$$\delta_i = l\delta_{i_0}(\frac{n_i}{N}).$$

Infection rate is integrated into the evolution of mutation process to epidemics in the urban population.

Medical treatment or quarantine reduces the number of the infected individuals in the urban population. These prevention measures can be interpreted as control parameters in the system defined as $u = (u_1, u_2)$, here u_i are fractions of the infected which are quarantined or under intensive medical treatment. Recovered rates are inversely proportional to disease duration $\overline{T}$, hence $\sigma_i = \frac{1}{\overline{T}}$.

The objective function: We will minimize the overall cost in time interval $[0, T]$. At any given t following costs exist in the system: $f_1(I_1(t)), f_2(I_2(t))$ these are treatment costs, $g(R(t))$ is benefit rate, $h_1(u_1(t)), h_2(u_2(t))$ are costs for medical measures (i.e. quarantine) that help to reduce epidemic spreading, k_{I_1}, k_{I_1}, k_R represent the costs and benefit for invective and recovered in the end of the epidemic. Here functions $f_i(t)$ are non-decreasing and twice-differentiable, convex functions, such as $f_i(0) = 0$, $f_i(I_i) > 0$ for $I_i > 0, i = 1, 2$, $g(t)$ is non-decreasing and differentiable function and $g(0) = 0$, $h_i(u_i(t))$ is twice-differentiable and increasing function in $u_i(t)$ such as $h_i(0) = 0$, $h_i(x) > 0$, $i = 1, 2$ when $u_i > 0$.

Aggregated system costs is given by

$$\begin{array}{l} J = \int_0^T f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + \\ h_1(u_1(t)) + h_2(u_2(t))dt + k_{I_1} I_1(T) + \\ k_{I_1} I_2(T) - k_R R(T) \end{array} \tag{3}$$

and the optimal control problem is to minimize the cost, i.e.,

$$\min_{\{u_1, u_2\}} J$$

To simplify the analysis, we consider the case where $k_{I_1} = k_{I_1} = k_R = 0$.

In previous paragraph, we assume that as a control parameters which help to reduce numbers of infected in human population, medical treatment or isolation can be considered, then define variable $u = (u_1, u_2)$ as control $0 \le u_1(t) \le 1$, $0 \le u_2(t) \le 1$, for all t.

IV. Optimal control

We use Pontryagin's Maximum principle to solve optimal control problem and define as $u = (u_1, u_2)$ optimal solution to the problem. Consider Hamiltonian H and adjoint functions λ_S, λ_{I_1}, λ_{I_r}, λ_R, λ_{x_1} as follows:

$$\begin{array}{l} H = f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + h_1(u_1(t)) + \\ \quad h_2(u_2(t)) + (\lambda_{I_1} - \lambda_S)\delta_1 S I_1 + \\ \quad (\lambda_{I_2} - \lambda_S)\delta_2 S I_2 + (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + \\ \quad (\lambda_R - \lambda_{I_2})\sigma_2 I_2 - (\lambda_{I_1} - \lambda_R) I_1 u_1 - \\ \quad (\lambda_{I_2} - \lambda_R) I_2 u_2. \end{array} \tag{4}$$

Here we use condition $R = 1 - S - I_1 - I_2$.
Let construct adjoint system:

$$\begin{array}{l} \dot{\lambda}_{I_1}(t) = -\frac{\partial H}{\partial I_1} = -f_1'(I_1) + \lambda_S \delta_1 S - \\ \qquad\qquad \lambda_{I_1}(\delta_1 S - \sigma_1) - \lambda_R \sigma_1; \\ \dot{\lambda}_{I_2}(t) = -\frac{\partial H}{\partial I_2} = -f_2'(I_2) + \lambda_S \delta_2 S - \\ \qquad\qquad \lambda_{I_2}(\delta_2 S - \sigma_2) - \lambda_R \sigma_1; \\ \dot{\lambda}_S(t) = -\frac{\partial H}{\partial S} = -\lambda_S(-\delta_1 I_1 - \delta_2 I_2) - \lambda_{I_1}\delta_1 I_1; \\ \dot{\lambda}_R(t) = -\frac{\partial H}{\partial R} = (g'(R)); \end{array} \tag{5}$$

with the transversality conditions:

$$\lambda_{I_1}(T) = 0,\ \lambda_{I_2}(T) = 0,\ \lambda_S(T) = 0,\ \lambda_R(T) = 0 \tag{6}$$

According to Pontryagin's Maximum Principle [14], [10] here exist continuous and piecewise continuously differentiable co-state functions λ_i that at every point $t \in [0,T]$ where u_1 and u_2 is continuous, satisfy (5) and (6). Also:

$$(u_1,u_2) \in arg \min_{\underline{u}_1,\underline{u}_2 \in [0,1]} H(\overline{p},(S,I_1,I_2,R),(\underline{u}_1,\underline{u}_2)) \quad (7)$$

V. Structure of optimal control

Based on previous research [10], [14], in this section we show that an optimal control $u(t) = (u_1(t), u_2(t))$ has following structure:

Proposition 5.1: The following statements hold for the optimal control problem described in Section IV:

- If $h_i(\cdot)$ are concave then

$$u(t) = (u_1(t),u_2(t)) = \begin{cases} (1,1), \text{ for } 0 < t < t_1; \\ (0,0), \text{ for } t_1 < t < T. \end{cases}$$

- If $h_i(\cdot)$ is strictly convex, then exists t_0, t_1, $0 < t_0 < t_1 < T$:

$$u_i(t) = \begin{cases} 0, \phi_i \le h_i'(0), \ i = 1,2; \\ h'^{-1}(\phi_i), \ h_i'(0) < \phi_i \le h_i'(1), \ i = 1,2; \\ 1, \ h_i'(1) < \phi_i, \ i = 1,2. \end{cases}$$

Proof:

Define functions ϕ_i as:

$$\phi_1 = (\lambda_{I_1} - \lambda_R) I_1, \phi_2 = (\lambda_{I_2} - \lambda_R) I_2$$

Rewrite Hamiltonian in terms of function ϕ

$$\begin{array}{l} H = (f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + \\ (\lambda_{I_1} - \lambda_S)\delta_1 S I_1 + \\ (\lambda_{I_2} - \lambda_S)\delta_2 S I_2 + (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + \\ (\lambda_R - \lambda_{I_2})\sigma_2 I_2 + \\ (h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2). \end{array} \quad (8)$$

For any admissible control u_1, u_2 and according to (7) for all $t \in [0,T]$

$$\begin{array}{l} [(h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2)] \le \\ h_1(\widetilde{u}_1(t)) - \phi_1 \widetilde{u}_1) + (h_2(\widetilde{u}_2(t)) - \phi_2 \widetilde{u}_2), \end{array} \quad (9)$$

then we obtain

$$\begin{array}{l} (u_1(t),u_2(t)) \in \\ \arg \min\limits_{\substack{x \in [0,1], \\ y \in [0,1]}} (h_1(x) - \phi_1 x) + (h_2(y) - \phi_2 y). \end{array} \quad (10)$$

$$\begin{array}{l} \min\limits_{u_1,u_2} [(h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2)] \\ = \min\limits_{u_1}(h_1(u_1(t)) - \phi_1 u_1) + \min\limits_{u_2}(h_2(u_2(t)) - \phi_2 u_2). \end{array}$$

Since $u_1 = u_2 = 0$ are admissible control, hence using (9), we obtain

$$\begin{array}{l} (h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2) \le \\ (h_1(0) - \phi_1 0) + (h_2(0) - \phi_2 0) = 0, \text{for all } t. \end{array} \quad (11)$$

To complete the proof of proposition we consider auxiliary lemma.

Lemma 5.2: Functions ϕ_i, $i = 1,2$ are decreasing functions of t, for all $t \in [0,T]$.

Proof. (Lemma 5.2)

The state and co-state functions are differentiable functions, then ϕ_i also differentiable functions at each time t, $t \in [0,T]$ at which functions u_1, u_2 are continuous. We have to show that $\dot{\phi}_i < 0$ at each time t.

Consider function ϕ_1:

$$\begin{array}{l} \dot{\phi}_1 = -(f_1'(I_1) - (\lambda_2 - \lambda_1)\delta_1 S - \\ \quad (\lambda_4 - \lambda_2)\sigma_1 - g'(R))I_1 - \\ \quad (\lambda_4 - \lambda_2)(\delta_1 S I_1 - \sigma_1 I_1 - I_1 u_1), \end{array} \quad (12)$$

and likewise, ϕ_2:

$$\begin{array}{l} \dot{\phi}_2 = -(f_2'(I_2) - (\lambda_3 - \lambda_1)\delta_2 S - \\ \quad (\lambda_3 - \lambda_1)\sigma_2 - \sigma_2 - g'(R))I_2 - \\ \quad (\lambda_4 - \lambda_2)(\delta_2 S I_2 - \sigma_2 I_2 - I_2 u_2). \end{array} \quad (13)$$

Here $f_1'(I_1) \ge 0$, $f_2'(I_2) \ge 0$, $g'(R) \ge 0$, $\delta_i \ge 0$, $I_1, I_2, S, R \ge 0$, $\alpha_i \ge 0$ then right hand side of expressions (12) and (13) are negative. The proof of lemma is completed.

Now we return to proposition 5.1 and consider two cases of cost functions $h_i(u_i), i = 1,2$.

1. *$h_i(\cdot)$ is concave.*

Let h_1 and h_2 be concave ($h_1'' < 0, h_2'' < 0$), then $(h_1(x) - \phi_1 x)$ and $(h_2(y) - \phi_2 y)$ are concave functions of x and y. For any time t the unique mimimum is either in $x = 0$ or $x = 1$ ($y = 0$ or $y = 1$). Then

$$u = (u_1,u_2) = \begin{cases} (0,0), \phi_1 + \phi_2 < h_1(1) + h_2(1), \\ (1,1), \ \phi_1 + \phi_2 > h_1(1) + h_2(1). \end{cases} \quad (14)$$

There can be at most one t at which $\phi_1(t) + \phi_2(t) = h_1(1) + h_2(1)$ according to Theorem of Intermediate value. As far as $\phi_i, i = 1,2$ are decreasing functions, hence if such t exists, say t_1, then $\phi_1 + \phi_2 > h_1(1) + h_2(1)$ for time interval $[0,t_1]$ and $\phi_1 + \phi_2 < h_1(1) + h_2(1)$ in $[t_1,T]$. For values $k_{I_1} = k_{I_1} = k_R = 0$, we have that $\phi_i(T) = 0$, $h_i(1) > 0$.

2. *$h_i(\cdot)$ is strictly convex.*

When $h_i(\cdot)$ are strictly convex ($h_i'' > 0$) then $\frac{\partial}{\partial x}(h_1(x) - \phi_1 x) \mid_{x=x_1} = 0$ and $\frac{\partial}{\partial y}(h_2(y) - \phi_1 y) \mid_{y=y_1} = 0$ at a $x \in [0,1]$ or $y \in [0,1]$, then $u_1(t) = x_1$ and $u_2(t) = y$, else $u_1(t) \in \{0,1\}$ and $u_2(t) \in \{0,1\}$. Then,

$$u_i = \begin{cases} 0, \phi_i \le h_i'(0), \ i = 1,2, \\ h'^{-1}(\phi_i), \ h_i'(0) < \phi_i \le h_i'(1), \ i = 1,2, \\ 1, \ h_i'(1) < \phi_i, \ i = 1,2. \end{cases} \quad (15)$$

function ϕ_i, h_i', u_i is continuous at all $t \in [0,T]$. In this case h_i is strictly convex and h_i' is strictly increasing function, so $h'(0) < h'(1)$. Thus there exists such points t_0, t_1, $0 < t_0 < t_1 < T$ such as conditions(15) are satisfied, according to ϕ_i is decreasing function.

From lemma (5.2) we need to check that multipliers $(\lambda_{I_1} - \lambda_S)$, $(\lambda_{I_2} - \lambda_S)$, $(\lambda_R - \lambda_{I_1})$ in equations (12) and (13) are non-negative.

Lemma 5.3: For all $0 \le t \le T$, we have $(\lambda_{I_1} - \lambda_S) > 0$, $(\lambda_{I_2} - \lambda_S) > 0$, $(\lambda_R - \lambda_{I_1}) > 0$

Proof of the lemma 5.3 is based on the next two properties.

Property 5.4: Let $w(t)$ be a continuous and piecewise differential function of t. Let $v(t_1) = L$ and $w(t) > L$ for all $t \in (t_1, \dots, t_0]$. Then $w(t_1^+) \geq 0$. Where $w(t_1^+) = \lim\limits_{x \to x_0} v(x)$.

Property 5.5: For any convex and differentiable function $y(x)$, which is 0 at $x = 0$, $y'(x)x - y(x) \geq 0$ for all $x \geq 0$.

VI. Numerical simulations

In this section, we present numerical simulations which are used to illustrate the results of theorems. We use following model's parameters: iteration step is $h = 0,01$, scale factor for virus dynamics is $\varepsilon = 100$, intensive rate of transition from susceptible to infected (I_1), $\delta_1 = 0,0005$, intensive rate of transition from susceptible to infected (I_2), $\delta_2 = 0,0016$, intensive rate of transition from infected (I_1) to recovered, $\sigma_1 = 1/15 = 0,0666$. Intensive rate of transition from infected (I_2) to recovered, $\sigma_2 = 1/7 = 0,1428$.

The figures below correspond to a concave functions $h_1(1)$, $h_2(2)$ and convex cases of theses functions. We use the following values: $S(0) = 950$, $I_1(0) = 30$, $I_2(0) = 20$, $R(0) = 0$; population size is $N = 1000$; epidemic duration is $T = 50$ as initial states for subpopulations S; I_1, I_2 and R and costs function $f_{I_1} = 10I_1$, $f_{I_2} = 20I_2$, $g(R) = 0,0025R$; if $h_i(u_i)$ are concave then $h_1(u_1) = 10u$, $h_2(u_2) = 20u$, if $h_i(u_i)$ are convex then $h_1(u_1) = 5u^2$, $h_1(u_1) = 10u^2$. Assume that typical duration of disease that is caused by virus V_1 is 15 days and duration of disease caused by virus V_2 is 7 days.

In Figures 2-4, we present tree variants of our model:

1) SIR model without virus mutation;
2) SIR model with virus mutation;
3) SIR model with virus mutation and application of control parameters.

In the first situation we observe that in epidemic peak we have number of infected $I_2 = 608$, $I_1 = 86$. Result of numerical simulation is presented in Figure 2.

In the second case, we consider epidemic process with the same initial states and assumption that virus mutates during epidemic period. We obtain a symmetric Nash equilibrium $(0,181818182, 0,818181818)$ for the virus mutation game. At the peak of epidemics, we have $I_1 = 607$, $I_2 = 184$. Result of the simulation is presented in Figure 3.

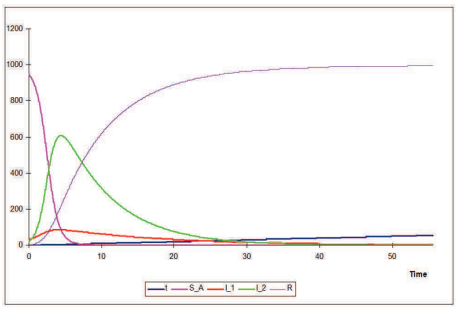

Fig. 2. SIR model without virus mutation.

To reduce the size of the infected population in urban population treatment treatment of quarantine are applied to the system. Results of numerical simulation with the same initial states and application of control parameters are presented in Figure 4. In epidemic peak we have $I_1 = 60$, $I_2 = 191$, hence we see that number of infected is reduced.

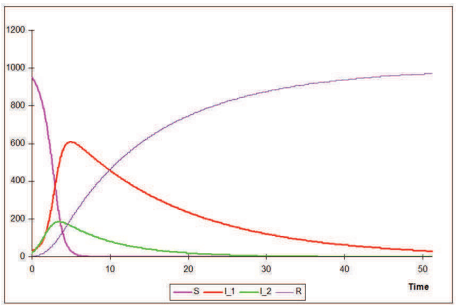

Fig. 3. SIR model with virus mutation.

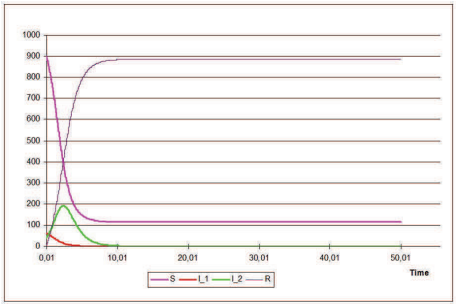

Fig. 4. SIR model with virus mutation and application of control. Functions $h_i,\ i = 1, 2$ are concave.

As a result of numerical simulation, we obtain that if we consider concave costs function $h_i(u_1)$ then switching time is $t_1 = 43.33$, if costs function $h_i(u_1)$ are strictly convex then time is $t_1 = 28.15$ for u_1 and $t_1 = 44.76$ for u_2.

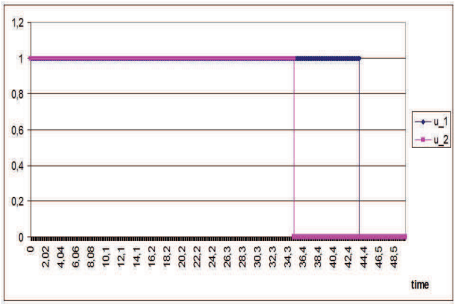

Fig. 5. Optimal control in SIR model with virus mutation. Functions h_i are concave, $t_1 = 43.34$.

Figures 5-7 demonstrate that optimal control $u = (u_1, u_2)$ has the same structure which is presented in Proposition 5.1. Switching time different and it depends on the cost function $h_i(u_1), i = 1, 2$.

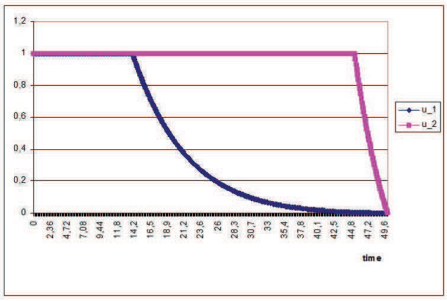

Fig. 6. Optimal control in SIR model with mutation.Functions h_i are strictly convex convex.For u_1: $t_1 = 26, 15$; for u_2: $t_1 = 44.77$.

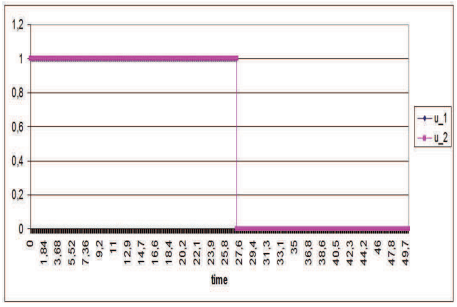

Fig. 7. SIR model with control parameters. Functions $h_i,\ i = 1, 2$ are concave. For u_1: $t_1 = 27.27$; for u_2: $t_1 = 27.27$.

VII. Conclusions

In this paper, we have studied an epidemic model that takes into account the evolutionary dynamics of virus mutations. The classical SIR epidemic dynamics are strongly coupled with the replicator dynamics of the virus. We have formulated an optimal control problem in which we seek to find an optimal treatment and quarantine strategies against the infection of two different types of viruses. Using Pontryagin's maximum principle, we have shown that, depending on the structure of the cost functions, the optimal control has a threshold structure. We have corroborated our results with numerical examples, observing different switching times for the control strategies under models with and without virus mutations. As future work, we would extend this work to multiple types of viruses and apply different evolutionary dynamics to model the process of virus mutations including imitative dynamics and best response dynamics.

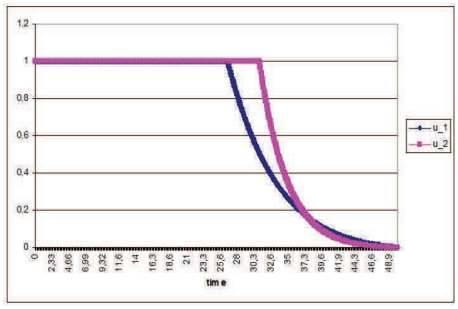

Fig. 8. SIR model with control parameters.Functions h_i are strictly convex.For u_1: $t_1 = 26.25$; for u_2: $t_1 = 30.88$.

References

[1] H. Behncke, *Optimal control of deterministic epidemics, Optim. Control Appl. Meth.*, no. 21, pp. 269–285, (2000).

[2] Bonhoeffer S., May R.M., Shaw G.M., Nowak M.A. *Virus dynamics and drug therapy*. Proc. Natl. Acad. Sci. USA 94: 6971-6976, (1997).

[3] Conn M. (ed.) *Handbook of Models for Human Aging* Elsevier Academic Press, London, (2006).

[4] P. J. Francis, "Optimal tax/subsidy combinations for the season," Journal of Economic Dynamic & Control, no. 28, pp. 2037–2054, (2004).

[5] Gjorgjieva J, Smith K., Chowell G., Sanchez F., Snyder J., Castillo-Chavez C. *The role of vaccination in the control of SARS. Mathematical biosciences and engineering.* Vol. 2, No. 4, (2005).

[6] Girvan M., Duncan S. Callaway, M. E. J. Newman, and S. H. Strogatz. *A simple model of epidemics with pathogen mutation*. Phys. Rev. E 65, 031915 (2002).

[7] Gubar E., Zhitkova E., Fotina L., Nikitina I. *Two Models of the Influenza Epidemic*. Contributions to game theory and management. Vol. V. Collected papers presented on the Fourth International Conference Game Theory and Management (GTM2011). SPb.: Graduate School of Management SpbU, pp. 107–120, (2012).

[8] Kermack W.O. and McKendrick A.G., *A contribution to the mathematical theory of epidemics,* in Proceedings of the Royal Society, Ser. A. V. 115, No. A771. p.700–721,(1927).

[9] Khatri S., Rael R., Hyman J., *The Role of Network Topology on the Initial Growth Rate of Influenza Epidemic*. Technical report BU-1643-M, (2003).

[10] Khouzani M. H. R., Sarkar S. and Altman E., *Optimal control of epidemic evolution,* in Proceedings of INFOCOM 2011, pp. 1683–1691, (2011).

[11] Khouzani M. H. R., Sarkar S., Altman E. *Maximum damage malware attack mobile wireless networks. Proceeding INFOCOM'10 Proceedings of the 29th conference on Information communications* pp. 749-757, 2010.

[12] Khouzani M. H. R., Sarkar S., Altman E. *Dispatch then stop: Optimal dissemination of security patches in mobile wireless networks.* CDC: 2354-2359, (2010).

[13] Maynard S., J. "Evolution and the Theory of Games." Cambridge University Press, (1982).

[14] Pontryagin L.S., V.G. Boltyanskii, R.V. Gamkrelidze et E.F. Mishchenko, *The Mathematical Theory of Optimal Processes*. Interscience, (1962).

[15] Smith A.M., Adler F.R., Ribeiro R.M., Gutenkunst R.N., McAuley J.L., et al. *Kinetics of Coinfection with Influenza A Virus and Streptococcus pneumoniae.* PLoS Pathog 9(3): e1003238. doi:10.1371/journal.ppat.1003238. (2013).

[16] Taylor, P. D. and Jonker, L. B., *Evolutionarily stable strategies and game dynamics, Math. Biosci.*, vol. 40, 145-156, (1978).

[17] Weibull J. *Evolutionary Game Theory*, The M.I.T. Press, Cambridge, MA, (1995).

[18] Wickwire K. H. *A note on the optimal control of carrier-borne epidemics* , *J. Appl. Probl.*, no. 12, pp.565–346, (1975).