Optimal Control of Influenza Epidemic Model with Virus Mutations

Gubar Elena and Quanyan Zhu

Abstract Different 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 SIR model does not capture the mutations of viruses, and hence the model is not sufficient to study epidemics where the virus mutates at the same time scale 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 SIR model with replicator dynamics used for describing virus mutations. We formulate an optimal control problem to study the optimal strategies for medical treatment and quarantine decisions. We obtain structural results for the optimal strategies and use numerical examples to corroborate our results.

Keywords: Evolutionary game dynamics, virus mutations, replicator dynamics, SIR epidemic model, optimal control, dynamic games, control of epidemics

1 Introduction

An epidemic of infectious disease occurs when virus population undergoes genetic mutations or new species of viruses are introduced into host population, and the host immunity to that change in the virus population is suddenly reduced below certain threshold. Hence, the epidemic modeling should take into account not only the population dynamics of the host population but also those of the viruses. In traditional epidemiological models, differential equations are used to capture the dynamic evolution of different classes of host populations. In particular, the susceptible (S) is the class of people who are not infected; the infected (I) is the class of people having the disease; the removed or recovered (R) represents dead or immune people. The commonly used SIR model [1, 2] is used to describe the population migrations between these three classes of models. In order to capture the interdependencies between virus and host populations, we establish a system framework that combines the SIR model with evolutionary models that describe virus mutations.

In this work, we study influenza epidemic in urban populations. We analyze the evolutionary model for virus mutations together with SIR models for evolution of 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

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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. 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 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 2, we discuss related work to our model. Section 3 presents the evolutionary model of viruses. In Section 4, we establish the epidemic model for the urban population. In section 5, we use Pontryagin's maximum principle to find the optimal control and present structural results of the optimal control problem. In section 6, we use numerical simulation to illustrate our results. The paper is concluded in Section 7.

2 Related Works

Recent literature has seen a surge of interest in using optimal control and game-theoretic methods to study disease control of influenza for public health. This research problem can be traced back to [3], where an SIR-type of mathematical framework has been proposed to study the epidemic spread in a homogeneous population. It provides a deterministic dynamical system model as the mean field approximation of the underlying stochastic evolution of the host subpopulations. In [4], a control problem is formulated for a model of carrier-borne epidemic model, and it has been shown the optimal control effort switches at maximum once between the maximum and the minimum control effort. In [5], many variants of optimal control models of SIR-epidemics are investigated for the application of medical vaccination and health promotion campaigns. In [6], a dynamic SIR epidemic model is used to identify the optimal vaccination policy mixes for the flue season.

Epidemic models have also been used in computer science and engineering to describe the temporal evolution of worm propagation in computer networks. Engineering methods, such as stochastic system analysis and optimal control methods, have been applied to provide insights on the epidemic spread as well as disease control policies for protecting the population with quarantine and removal. In [7], a sequential hypothesis testing is adopted to detect a worm epidemic propagation over the Internet under a stochastic density-dependent Markov jump process propagation model. In [8, 9], optimal control methods have been used to study the class of epidemic models in mobile wireless networks, and Pontryagin's maximum principle is used to quantify the damage that the malware can inflict on the network by deploying optimum decision rules.

Game-theoretic approaches have also been used to analyze the strategic interactions between malicious worms and the system under attack. In [10], a virus protection game has been proposed based on two-state epidemic models for N nodes and the characterization of the equilibrium focus on the steady state of the response. In [11], static and dynamic game frameworks have been used to design equilibrium revocation strategies for defending sensor networks from node capturing and cloning attacks. It has been shown that the $N+1$ nonzero-sum differential game framework is equivalent to a zero-sum differential game between a team of N attackers and the system.

Different from the work done in the past, this paper considers a coupled system framework composed of the SIR epidemic model and the evolutionary dynamic model for virus mutation. This framework is motivated by the fact that the epidemic spread of the virus can facilitate the virus mutation, strengthening the virulence of the virus, which will in turn expedite the spread and worsen the epidemics. The SIR epidemic model with virus mutations can capture this complex interactions between the virus and the host, and allows us to explain more complex phenomena through analysis.

3 Evolutionary Model of Virus Mutation

Infection decease, such as influenza and SARS, is an urgent public health problem in modern urban environment. Influenza spreads faster, especially in large urban populations and influences the lifestyle and working facilities of people. The occurrence of epidemics depends on many factors such as the size of human population, virus strain and virulence, and it has become important to use effective tools to reduce their influence on human population [12], [13], [14]. Mathematical model of virus infection in a population can be used to study those factors, which influence the epidemic growth for improving existing treatment and evaluating new effective prevention measures and treatment. In earlier research in the literature, 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 Fig. 1. At the top level, two different types of influenza virus compete to infect the host for continuing their life cycles, and thereby leading to the spread of epidemics in human population. The total population will contain several infected subpopulations, which correspond to different virus types. On the bottom level, the human population is divided into subpopulations: the susceptible (S), the infected (I) and the recovered (R). Spreading of the viruses can be controlled with help of prevention measures, such as medical treatment or isolation of infected individuals of population. Thus, at this level, we consider SIR model with those control parameters.

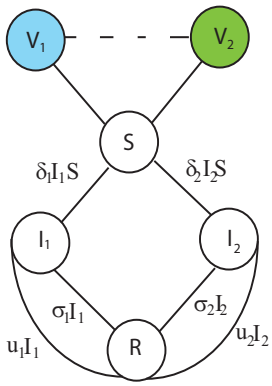

Fig. 1 Transition rule: The scheme describes the reaction of human population to the virus mutation. We assume that the epidemic process can be controlled using treatment or quarantine methods. These measures can de considered as control parameters in the system, and used to reduce the size of the infected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

At the top 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 compete for human organisms, 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 that V_1 dominates virus 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 survivability of the virus among its infected population (e.g. human beings). The life cycle of viruses requires a host organism and occupation of such organism leads to energy costs. Hence the virus payoff J_i is composed of two components: 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 the fraction of corresponding virus' types circulating in population. Thereby virus population

state is defined as value $x(t) = (x_1(t), x_2(t))$, $x_1 + x_2 = 1$, here $x_i(t) = \frac{p_i(t)}{M}, i = 1,2$, component $p_i(t)$ is the number of replicas of virus V_i, M is virus population size.

Depending on the virus strength, the number of people infected by different virus types will be different. We need two flows of epidemic processes in human population to describe our model to describe the population. We use I_1 to denote the population state for the subpopulation infected by type 1 virus, and I_2 is the state for the subpopulation 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 of virus V_1 meets 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 host organism, and achieve a utility of b_1 with probability $1/2$ if it succeeds in occupation.
- if virus V_1 meets a virus V_2, then virus V_1 obtains a payoff of b_1 and V_2 obtains a payoff of 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 [15], we compare the payoff of the i-th pure strategy with the 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 the population $u : \mathbb{R}^2 \to \mathbb{R}$ is defined as

$$u(x,x) = \sum_{i=1}^{k} x_i u(e^i, x),$$

where $e^i \in \mathbb{R}^2, i = V_1, V_2$, is a vector with i-th element being one and 0 otherwise, indicating the i-th pure strategy; u is a continuous function. The payoff of the i-th pure strategy is defined by $u(e^i, x) = e^i Ax$, where A is the payoff matrix of current symmetric game, and $x_i(t)$ is fraction of virus V_i [16].

To describe evolution of virus we need to use system of differential equations, in current work, we focused on replicator dynamics [17] to describe changes of states in virus population.

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

where $\varepsilon \in \mathbb{R}_+$ is time scaling factor. Since the mutation process in virus population and epidemic process in human population may develop with different speed (e.g. virus can mutate faster than spreads in human population), ε can be used to describe such difference in the time scale of the two dynamics.

The stationary state of the system of differential equations (1) leads to symmetric Nash equilibrium [17]. Therefore, depending on the parameters b_i, C_i, the game has two asymmetric Nash equilibria $(1,0)$, $(0,1)$, corresponding to the strategies in which all population are being type V_1 and V_2, respectively; and one symmetric Nash equilibrium $(\overline{x}, \overline{x})$, 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 $a_1 = \frac{b_1-C_1}{2}$, $a_2 = \frac{b_2-C_2}{2} - b_1$. Symmetric case is more interesting since both virus types have influences on the human population.

4 Epidemic Process for Urban Population

Consider a total urban population of size N with two types of viruses circulate in the population during epidemic season. The human population is divided into four groups: the susceptible, the infected by virus V_1, the infected by virus V_2, and the recovered. The susceptible is a subpopulation of human being that are not infected by viruses but will be infected by one or both types of viruses, 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, and 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 infected by virus V_1 or V_2 belong to the infected subpopulation. The recovered subpopulation consists of people recovered from being infected. The mixing of urban populations allows viruses to spread quickly, and each person in the 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 has higher probability of success in spreading when interaction occurs between an infected individual and a susceptible individual.

4.1 Epidemic Dynamics

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 aresusceptible, 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 portions of the susceptible, the infected and the recovered in the population. 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 [3],[18] to describe the situation with two virus types:

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

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}

$$\delta_i = l\delta_{i_0}\left(\frac{n_{I_i}}{N}\right) = l\delta_{i_0} I_i.$$

In this work, changes in virus population influence on the parameters of SIR model, and therefore number of infected is a function of corresponding virus subpopulation x_j, $j = V_1, V_2$, $I_i(t) = I_i(x_i,t)$. We let $I_i(x_i,t)$ be linear and δ_i take the following form:

$$\delta_i = l\delta_{i_0} I_i(x_i,t).$$

Then SIR model can be rewritten as follows:

$$\begin{aligned}
\frac{dS}{dt} &= -\delta_1 S - \delta_2 S;\\
\frac{dI_1}{dt} &= \delta_1 S - \sigma_1 I_1 - u_1 I_1;\\
\frac{dI_2}{dt} &= \delta_2 S - \sigma_2 I_2 - u_2 I_2;\\
\frac{dR}{dt} &= (\sigma_1 + u_1) I_1 + (\sigma_2 + u_2) I_2;
\end{aligned} \tag{3}$$

In the model above, the infection rate is integrated into the evolution of mutation process to epidemics in the urban population.Medical treatment or quarantine isolation 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, $0 \le u_1(t) \le 1$, $0 \le u_2(t) \le 1$, for all t. Recovered rates are inversely proportional to disease duration $\overline{T}$, hence $\sigma_i = \frac{1}{\overline{T}}$.

4.2 Objective Function

In this work, 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 the benefit rate; $h_1(u_1(t)), h_2(u_2(t))$ are costs for medical treatments (i.e. quarantine or removal) that help to reduce the 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 $f_i(I_i)$ are non-decreasing and twice-differentiable, convex functions, i.e., $f_i(0) = 0$, $f_i(I_i) > 0$ for $I_i > 0, i = 1,2.$, $g(R)$ 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 $u_i > 0$.

The cost for the aggregated system is given by

$$J = \int_0^T f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + h_1(u_1(t)) + h_2(u_2(t))dt + k_{I_1} I_1(T) + k_{I_1} I_2(T) - k_R R(T) \tag{4}$$

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 $k_{I_1} = k_{I_1} = k_R = 0$.

5 Optimal Control of Epidemics

We use Pontryagin's maximum principle [20], to find the optimal control $u = (u_1, u_2)$ to the problem described above in Section 4. Define the associated Hamiltonian H and adjoint functions λ_S, λ_{I_1}, λ_{I_r}, λ_R as follows:

$$\begin{aligned} H = {} & f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + h_1(u_1(t)) + h_2(u_2(t)) + (\lambda_{I_1} - \lambda_S)\delta_1 S I_1 + \\ & (\lambda_{I_2} - \lambda_S)\delta_2 S I_2 + (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + (\lambda_R - \lambda_{I_2})\sigma_2 I_2 - (\lambda_{I_1} - \lambda_R) I_1 u_1 - (\lambda_{I_2} - \lambda_R) I_2 u_2. \end{aligned} \tag{5}$$

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

$$\begin{aligned} \dot{\lambda}_S(t) &= -\tfrac{\partial H}{\partial S} = -\lambda_S(-\delta_1 I_1 - \delta_2 I_2) - \lambda_{I_1}\delta_1 I_1; \\ \dot{\lambda}_{I_1}(t) &= -\tfrac{\partial H}{\partial I_1} = -f_1'(I_1) + \lambda_S \delta_1 S - \lambda_{I_1}(\delta_1 S - \sigma_1) - \lambda_R \sigma_1; \\ \dot{\lambda}_{I_2}(t) &= -\tfrac{\partial H}{\partial I_2} = -f_2'(I_2) + \lambda_S \delta_2 S - \lambda_{I_2}(\delta_2 S - \sigma_2) - \lambda_R \sigma_1; \\ \dot{\lambda}_R(t) &= -\tfrac{\partial H}{\partial R} = (g'(R)); \end{aligned} \tag{6}$$

with the transversality conditions given by

$$\lambda_{I_1}(T) = 0,\ \lambda_{I_2}(T) = 0,\ \lambda_S(T) = 0,\ \lambda_R(T) = 0 \tag{7}$$

According to Pontryagin's maximum principle, there 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 (6) and (7). In addition, we have

$$(u_1, u_2) \in \arg \min_{\underline{u}_1, \underline{u}_2 \in [0,1]} H(\overline{\lambda}, (S, I_1, I_2, R), (\underline{u}_1, \underline{u}_2)). \tag{8}$$

5.1 Structure of Optimal Control

Based on previous research [9],[19], [20] in this subsection, we show that an optimal control $u(t) = (u_1(t), u_2(t))$ has following structural results.

Proposition 1 *The following statements hold for the optimal control problem described in Section 4:*

- *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. The proof of Proposition 1 will require an auxiliary Lemma 1 and it will be discussed in detail in Section 5.2. Before stating Lemma 1, first we define functions ϕ_i as follows.

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

Rewrite the Hamiltonian in terms of function ϕ and we obtain

$$\begin{aligned} H = {} & (f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + (\lambda_{I_1} - \lambda_S)\delta_1 SI_1 + (\lambda_{I_2} - \lambda_S)\delta_2 SI_2 + (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + \\ & (\lambda_R - \lambda_{I_2})\sigma_2 I_2 + (h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2). \end{aligned} \tag{9}$$

For any admissible control u_1, u_2 and according to (8) for all $t \in [0,T]$

$$[(h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2)] \le h_1(\widetilde{u}_1(t)) - \phi_1 \widetilde{u}_1) + (h_2(\widetilde{u}_2(t)) - \phi_2 \widetilde{u}_2), \tag{10}$$

then, we obtain

$$(u_1(t), u_2(t)) \in \arg \min_{x \in [0,1], y \in [0,1]} (h_1(x) - \phi_1 x) + (h_2(y) - \phi_2 y). \tag{11}$$

We observe that

$$\min_{u_1,u_2}[(h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2)] = \min_{u_1}(h_1(u_1(t)) - \phi_1 u_1) + \min_{u_2}(h_2(u_2(t)) - \phi_2 u_2).$$

Since $u_1 = u_2 = 0$ are admissible control, hence using (10), we obtain

$$(h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2) \le (h_1(0) - \phi_1 0) + (h_2(0) - \phi_2 0) = 0, \quad \text{for all } t. \tag{12}$$

To prove Proposition 1, we consider the following auxiliary lemma.

Lemma 1. *Functions $\phi_i,\ i = 1,2$ are decreasing functions of t, for $t \in [t_0, T]$, $t_0 \ge t \ge 0$, while*

$$\delta_i SI_i - \sigma_i I_i \ge u_i, i = 1,2. \tag{13}$$

Proof:

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 $t \in [t_0, T]$, $t_0 \ge t \ge 0$. Consider function ϕ_1 given by

$$\dot{\phi_1} = -(f_1'(I_1) - (\lambda_{I_1} - \lambda_S)\delta_1 S - (\lambda_R - \lambda_{I_1})\sigma_1 - g'(R))I_1 - (\lambda_R - \lambda_{I_1})(\delta_1 SI_1 - \sigma_1 I_1 - I_1 u_1), \tag{14}$$

and likewise, ϕ_2 as follows:

$$\dot{\phi_2} = -(f_2'(I_2) - (\lambda_{I_2} - \lambda_S)\delta_2 S - (\lambda_R - \lambda_{I_2})\sigma_2 - g'(R))I_2 - (\lambda_R - \lambda_{I_1})(\delta_2 S I_2 - \sigma_2 I_2 - I_2 u_2). \quad (15)$$

Here, $f_1'(I_1) \geq 0$, $f_2'(I_2) \geq 0$, $g'(R) \geq 0$, $\delta_i \geq 0$, $I_1, I_2, S, R \geq 0$, then right hand side of expressions (14) and (15) are negative, if conditions $\delta_1 S I_1 - \sigma_1 I_1 \geq u_1$ and $\delta_2 S I_2 - \sigma_2 I_2 \geq u_2$ are satisfied, otherwise functions ϕ_i are increasing. The term $\delta_i S I_i - \sigma_i I_i \geq u_i \geq 0$, $i = 1,2$ can be interpreted as a condition for the beginning of the epidemic, see [3]. The proof of Lemma 1 is completed.

5.2 Proof of Proposition 1

In this subsection, we prove proposition 1 under two cases of cost functions $h_i(u_i), i = 1,2$.

5.2.1 $h_i(\cdot)$ are 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

$$u = (u_1, u_2) = \begin{cases} (0,0), \phi_1 + \phi_2 < h_1(1) + h_2(1), \\ (1,1),\ \phi_1 + \phi_2 > h_1(1) + h_2(1). \end{cases} \quad (16)$$

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, while conditions $\delta_i S I_i - \sigma_i I_i \geq u_i$, $i = 1,2$ are satisfied, hence if such t exists, say t_1, then $\phi_1 + \phi_2 > h_1(1) + h_2(1)$ for time interval $[t_0, t_1]$ and $\phi_1 + \phi_2 < h_1(1) + h_2(1)$ in $[t_1, T]$. If conditions (13) are broken, then $\phi_1 + \phi_2 < h_1(1) + h_2(1)$ for time interval $[0, t_0]$. For values $k_{I_1} = k_{I_1} = k_R = 0$, we have that $\phi_i(T) = 0$, $h_i(1) > 0$.

5.2.2 $h_i(\cdot)$ are 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,

$$u_i = \begin{cases} 0, \ \ \phi_i \leq h_i'(0),\ i = 1,2; \\ h'^{-1}(\phi_i), \ \ h_i'(0) < \phi_i \leq h_i'(1),\ i = 1,2. \\ 1, \ \ h_i'(1) < \phi_i,\ i = 1,2 \end{cases} \quad (17)$$

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(17) and (13) are satisfied, and according to ϕ_i is decreasing function. In time interval where $\delta_i S I_i - \sigma_i I_i < u_i, i = 1,2$ then ϕ_i are increasing functions and conditions (17) will be rewritten. There may exist such time interval $[0, t_0)$ that $u_i = 0$ and $\phi_i \leq h_i'(0),\ i = 1,2$, and then for time interval $[t_0, T]$ conditions (17) continue to be satisfied.

Using the auxiliary Lemma 2 below, we complete the proof of Proposition 1. From Lemma 1, we need to check that multipliers $(\lambda_{I_1} - \lambda_S)$, $(\lambda_{I_2} - \lambda_S)$, $(\lambda_R - \lambda_{I_1})$ in equations (14) and (15) are non-negative.

Lemma 2. *For all $0 \leq t \leq T$, we have $(\lambda_{I_1} - \lambda_S) > 0$, $(\lambda_{I_2} - \lambda_S) > 0$, $(\lambda_R - \lambda_{I_1}) > 0$.*

Property 1. Let $w(t)$ be a continuous and piecewise differential function of t. Let $w(t_1) = L$ and $w(t) > L$ for all $t \in (t_1, \ldots, t_0]$. Then $w(t_1^+) \geq 0$, where $w(t_1^+) = \lim_{x \to x_0} v(x)$.

Property 2. For any convex and differentiable function $y(x)$, which is 0 at $x = 0$, $y'(x)x - y(x) \geq 0$ for all $x \geq 0$.

Proof: We first prove the case for $t = T$ and then for $t < T$. **Step 1.** At time T, we have $(\lambda_{I_1}(T) - \lambda_S(T)) = 0$, $(\lambda_{I_2}(T) - \lambda_S(T)) = 0$, and $(\lambda_R(T) - \lambda_{I_1}(T)) = 0$ according to (7). $\dot{\lambda}_{I_1}(T) - \dot{\lambda}_S(T) = -f_1'(I_1(T)) < 0$ and by analogy

$\dot{\lambda}_{I_2}(T) - \dot{\lambda}_S(T) = -f_2'(I_2(T)) < 0$ and $\dot{\lambda}_R(T) - \dot{\lambda}_{I_1(T)} = f_1'(I_1(T)) + g(R(T)) > 0$, therefore expressions $(\lambda_{I_1}(T) - \lambda_S(T))$, $(\lambda_{I_2}(T) - \lambda_S(T))$, $(\lambda_R(T) - \lambda_S I_1(T))$ are positive in an open interval $(0,T)$.

Step 2. (Proof by contradiction).

Let $t^* < T$ be the last instant moment at which one of the inequality constraints are performed:

Case I. In this case, we will prove that $(\lambda_{I_1}(t) - \lambda_S(t)) > 0$. Suppose that $(\lambda_{I_1}(t) - \lambda_S(t)) = 0$, $(\lambda_{I_2}(t) - \lambda_S(t)) = 0$ and $(\lambda_R(t) - \lambda_{I_1}(t)) > 0$ then

$$\dot{\lambda}_{I_1}(t^*) - \dot{\lambda}_S(t^*) = f_1'(I_1) - (\lambda_{I_1} - \lambda_S)\delta_1 S - (\lambda_R - \lambda_{I_1})\sigma_1 - (\lambda_S - \lambda_{I_1})\delta_1 I_1 - (\lambda_S - \lambda_{I_2})\delta_2 I_2,$$

and hence we obtain that $(\dot{\lambda}_{I_1}(t^*) - \dot{\lambda}_S(t^*)) < 0$. This contradicts *Property 1* for function $(\lambda_{I_1}(t^*) - \lambda_S(t^*))$ which means that $(\lambda_{I_1}(t^*) - \lambda_S(t^*)) > 0$.

Now let $(\lambda_R(t) - \lambda_{I_1}(t)) = 0$ and $(\lambda_R(t) - \lambda_{I_2}(t)) = 0$ and $(\lambda_S(t) - \lambda_{I_1}(t)) > 0, (\lambda_S(t) - \lambda_{I_2}(t)) > 0$.

$$\begin{aligned}\dot{\lambda}_{I_1}(t^{*+}) - \dot{\lambda}_S(t^{*+}) &= (-f_1'(I_1) + \lambda_S\delta_1 S - \lambda_{I_1}(\delta_1 S - \sigma_1) - \lambda_R\sigma_1) - (-\lambda_S(-\delta_1 I_1 - \delta_2 I_2) - \lambda_{I_1}\delta_1 I_1)\\ &= -f_1'(I_1) - (\lambda_{I_1} - \lambda_S)\delta_1 S - (\lambda_R - \lambda_{I_1})\sigma_1 + (\lambda_{I_1} - \lambda_S)\delta_1 I_1 + (\lambda_{I_2} - \lambda_S)\delta_2 I_2\\ &= -f_1'(I_1) - (\lambda_{I_1} - \lambda_S)\delta_1 S - (\lambda_R - \lambda_{I_1})\sigma_1 - (\lambda_S - \lambda_{I_1})\delta_1 I_1 - (\lambda_S - \lambda_{I_2})\delta_2 I_2.\end{aligned} \tag{18}$$

If $\delta_1 = 0$ and $\delta_2 = 0$ and $(\lambda_R(t) - \lambda_{I_1}(t)) > 0$ then $\dot{\lambda}_{I_1}(t^*) - \dot{\lambda}_S(t^*) < 0$ that contradicts *Property 1* for the functions $(\lambda_{I_1}(t^*) - \lambda_S(t^*))$ at time t^*, and also such moment t^* does not exist. Lemma 2 is proved in this case.

If $\delta_1 > 0$ and $\delta_2 > 0$, then the system of ODE is autonomous, and hence Hamiltonian and the control do not have dependence of the variable independent t.

$$H(S(t), I_1(t), I_2(t), R(t), u_1(t), u_2(t), \lambda_S(t), \lambda_{I_1}(t), \lambda_{I_2}(t), \lambda_R(t)) = constant. \tag{19}$$

From (5), we obtain

$$\begin{aligned}H = {} & f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + h_1(u_1(t)) + h_2(u_2(t)) + (\lambda_{I_1} - \lambda_S)\delta_1 S I_1 + (\lambda_{I_2} - \lambda_S)\delta_2 S I_2 +\\ & (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + (\lambda_R - \lambda_{I_2})\sigma_2 I_2 - (\lambda_{I_1} - \lambda_R) I_1 u_1 - (\lambda_{I_2} - \lambda_R) I_2 u_2.\end{aligned} \tag{20}$$

Since $g(R)$ is a non-decreasing function, then $g(R(T)) \geq g(R(t))$, we obtain

$$\begin{aligned}H - f_1(I_1(t)) + g(R(t) \geq {} & f_2(I_2(t)) + h_1(u_1(t)) + h_2(u_2(t)) + (\lambda_{I_1} - \lambda_S)\delta_1 S I_1 + (\lambda_{I_2} - \lambda_S)\delta_2 S I_2 +\\ & (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + (\lambda_R - \lambda_{I_2})\sigma_2 I_2 + (\lambda_R - \lambda_{I_1}) I_1 u_1 + (\lambda_R - \lambda_{I_2}) I_2 u_2 \geq 0.\end{aligned} \tag{21}$$

This follows from assumptions on functions $f_1(I_1)$ and $h_1(u_1)$, $h_2(u_2)$ such as $I_1(T) > 0$ then $f_1(I_1) > 0$ and $u_1(t) > 0$, $u_2(t) > 0$ then $h_1(u_1) \geq 0$, $h_2(u_2) \geq 0$.

From (9), we have

$$\begin{aligned}H = {} & (f_1(I_1(t)) + f_2(I_2(t)) - g(R(t)) + (\lambda_{I_1} - \lambda_S)\delta_1 S I_1 + (\lambda_{I_2} - \lambda_S)\delta_2 S I_2 + (\lambda_R - \lambda_{I_1})\sigma_1 I_1 + (\lambda_R - \lambda_{I_2})\sigma_2 I_2\\ & + (h_1(u_1(t)) - \phi_1 u_1) + (h_2(u_2(t)) - \phi_2 u_2).\end{aligned} \tag{22}$$

Therefore, we obtain

$$\begin{aligned}\dot{\lambda}_{I_1}(t) - \dot{\lambda}_S(t) = {} & -f_1'(I_1) + \frac{f_1(I_1(t)) + f_2(I_2(t)) - g(R(t) - H}{I_1} + \frac{(h_1(u_1(t)) - \phi_1 u_1)}{I_1} + \frac{(h_2(u_2(t)) - \phi_2 u_2)}{I_1} -\\ & (\lambda_S - \lambda_{I_2})\delta_2 S\tfrac{I_2}{I_1} - (\lambda_{I_2} - \lambda_R)\sigma_2\frac{I_2}{I_1} + (\lambda_{I_1} - \lambda_S)\delta_1 I_1 + (\lambda_{I_2} - \lambda_S)\delta_2 I_2\\ = {} & \frac{1}{I_1}(f_1(I_1) - f_1'(I_1)I_1) - \frac{1}{I_1}(H - f_2(I_2) + g(R)) + \frac{(h_1(u_1(t)) - \phi_1 u_1)}{I_1} + \frac{(h_2(u_2(t)) - \phi_2 u_2)}{I_1} -\\ & (\lambda_S - \lambda_{I_2})\delta_2 S\frac{I_2}{I_1} - (\lambda_{I_2} - \lambda_R)\sigma_2\frac{I_2}{I_1} - (\lambda_S - \lambda_{I_1})\delta_1 I_1 - (\lambda_S - \lambda_{I_2})\delta_2 I_2.\end{aligned} \tag{23}$$

Here $f_1(I_1)$ is convex increasing function and $f_1(0) = 0$, $I_1 > 0$ and $(f_1(I_1) - f_1'(I_1)I_1) \leq 0$, by *Property 2*. From (7), (18), (21) Then $\dot{\lambda}_{I_1}(t) - \dot{\lambda}_S(t) < 0$ and it contradicts *Property 1*, and part **I** of the lemma follows.

Case II. We have to prove that $(\lambda_{I_2}(t) - \lambda_S(t)) > 0$. This is a symmetric case to Case **I** Using the same reasoning, we obtain

$$\begin{aligned}\dot{\lambda}_{I_2}(t)-\dot{\lambda}_S(t) &= -f'(I_2)+(\lambda_S-\lambda_{I_2})\delta_2 S+(\lambda_{I_2}-\lambda_R)\sigma_2+(\lambda_{I_1}-\lambda_S)\delta_1 I_1+(\lambda_{I_2}-\lambda_S)\delta_2 I_2\\ &= \frac{1}{I_2}(f_2(I_2)-f_2'(I_2)I_2)-\frac{1}{I_2}(H-f_1(I_1)+g(R))+\frac{(h_1(u_1(t))-\phi_1 u_1)}{I_2}+\frac{(h_2(u_2(t))-\phi_2 u_2)}{I_2}-\\ &\quad (\lambda_S-\lambda_{I_1})\delta_1 S\frac{I_1}{I_2}-(\lambda_{I_1}-\lambda_R)\sigma_1\frac{I_1}{I_2}-(\lambda_S-\lambda_{I_2})\delta_2 I_2-(\lambda_S-\lambda_{I_1})\delta_1 I_1.\end{aligned} \tag{24}$$

Thus, we have $\dot{\lambda}_{I_2}(t)-\dot{\lambda}_S(t)<0$ that contradicts *Property 1*, and hence functions $(\lambda_{I_2}(t)-\lambda_S(t))>0$.
Case III. In this case, we will prove that $(\lambda_R(t)-\lambda_{I_1}(t))>0$ in similar way.

$$\begin{aligned}H-f_2(I_2(t))+g(R(t)\geq -f_1(I_1(t))+h_1(u_1(t))+h_2(u_2(t))+(\lambda_{I_1}-\lambda_S)\delta_1 SI_1+(\lambda_{I_2}-\lambda_S)\delta_2 SI_2+\\ (\lambda_R-\lambda_{I_1})\sigma_1 I_1+(\lambda_R-\lambda_{I_2})\sigma_2 I_2+(\lambda_R-\lambda_{I_1})I_1u_1+(\lambda_R-\lambda_{I_2})I_2u_2\geq 0\end{aligned} \tag{25}$$

This follows from assumptions on functions $h_1(u_1)$, $h_2(u_2)$ such as $I_1(T)>0$ then $f_1(I_1)>0$ and $u_1(t)>0$, $u_2(t)>0$ then $h_1(u_1)\geq 0$, $h_2(u_2)\geq 0$. Therefore, we obtain

$$\begin{aligned}\dot{\lambda}_R(t)-\dot{\lambda}_{I_1}(t) &= g'(R)+f_1'(I_1)-\lambda_{I_1}\delta_1 S+\lambda_{I_2}(\delta_1 S-\sigma_1)+\lambda_R\sigma_1\\ &= g'(R)+f_1'(I_1)+(\lambda_{I_1}-\lambda_S)\delta_1 S+(\lambda_R-\lambda_{I_1})\sigma_1\\ &= g'(R)+f_1'(I_1)+\frac{H}{I_1}-\frac{f_2(I_2)}{I_1}+\frac{1}{I_1}(f_1'(I_1)I_1-f_1(I_1))+\frac{g(R)}{I_1}+(\lambda_S-\lambda_{I_2})\delta_2 S\frac{I_2}{I_1}+\\ &\quad (\lambda_R-\lambda_{I_2})\sigma_2\frac{I_2}{I_1}-\frac{(h_1(u_1(t))-\phi_1 u_1)}{I_1}-\frac{(h_2(u_2(t))-\phi_2 u_2)}{I_1}.\end{aligned} \tag{26}$$

From (7), (18), (21), (12) , we obtain $\dot{\lambda}_R(t)-\dot{\lambda}_{I_1}(t)>0$ and by *Property 1* $\lambda_R(t)-\lambda_{I_1}(t)>0$, Lemma 2 follows. Together with lemma **1** proof of lemma **2** completes proof of proposition **1.**

5.3 Quadratic Cost Functions

In this subsection, we consider a particular case of Proposition 1, where the cost functions $h_i(u), i=1,2$ are quadratic, i.e.,

$$h_i(u)=a_0u_i^2+a_1u_i+a_2,\ \ a_0\neq 0. \tag{27}$$

Quadratic function is strictly convex if coefficient $a_0>0$, and we can apply the same arguments as in part **2** of Lemma 1. Consider $\frac{\partial}{\partial x}(h_i(x)-\phi_i x)\mid_{x=x_1}=0$ from Proposition 1, where $h_i(u)$ is defined as in (27), then we obtain

$$\frac{\partial}{\partial x}(h_i(x)-\phi_i x)\mid_{x=x_1}=\frac{\partial}{\partial x}(a_0u_i^2+a_1u_i+a_2-\phi_i x)\mid_{x=x_1}=2a_0u_i+a_1-\phi_i,$$

Hence we arrive at the following form of optimal control

$$u_i=\begin{cases}0, & \phi_i\leq h_i'(0),\ i=1,2;\\ \frac{\phi_i-a_1}{2a_0}, & h_i'(0)<\phi_i\leq h_i'(1),\ i=1,2.\\ 1, & h_i'(1)<\phi_i,\ i=1,2\end{cases} \tag{28}$$

Functions ϕ_i, h_i', u_i are continuous at all $t\in[0,T]$. In this case, h_i is strictly convex and h_i' is a 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 (28) and (13) are satisfied, and ϕ_i is decreasing function. If conditions (13) are broken then there may exist such time interval $[0,t_0)$ that $u_i=0$ and $\phi_i\leq h_i'(0),\ i=1,2$, and then for time interval $[t_0,T]$ conditions (28) continue to be satisfied.

6 Numerical Simulations

In this section, we present numerical simulations to corroborate our results. The system parameters are described as follows. Population size is $N=100000$, at initial time, the susceptible population $S(0)=99200$ individuals, the recovered population $R(0)=0$. We suppose that 0.04 percent of population are infected by virus V_1, i.e., $I_1(0)=400$,

and 0.03 percent of population are infected by virus V_2, i.e., $I_2(0) = 300$. Epidemic lasts for the period of 60 days. During the epidemic, people from the infected population incur costs for the treatment, and hence thereby we define costs functions as $f_{I_1} = 40I_1$, $f_{I_2} = 10I_2$, $g(R) = 0.05R$. For concave cost functions we used $h_1(u_1) = 10u_1$, $h_2(u_2) = 5u_2$ and for convex cost functions – $h_1(u_1) = 20u_1^2$, $h_1(u_1) = 10u_2^2$. The costs here are measured in same monetary units (m.u.), which can be in US dollars, Chinese RMB, or Euros depending on the context. We let the duration of disease caused by virus V_1 be 15 days, while the duration of disease caused by virus V_2 be 8 days. Clearly, virus V_1 is stronger than virus V_2.

The auxiliary parameters of the model are given as follows. We choose iteration step $h = 0.0115$; the scale factor for virus dynamics $\varepsilon = 100$; the transition rate from the susceptible to the infected population I_1, $\delta_{1_0} = 0.000006$; the transition rate from the susceptible to the infected population I_2, $\delta_{2_0} = 0.000004$; the transition rate from the infected population I_1 to the recovered, $\sigma_1 = 1/15 = 0.066666667$; and the transition rate from the infected I_2 to the recovered, $\sigma_2 = 1/8 = 0.125$.

In Figs. 2-4, we present three variants of our model:

1. Original SIR model without virus mutation;
2. SIR model with virus mutation process;
3. SIR model with virus mutation and application of control, two modifications which depend on the costs functions properties are considered.

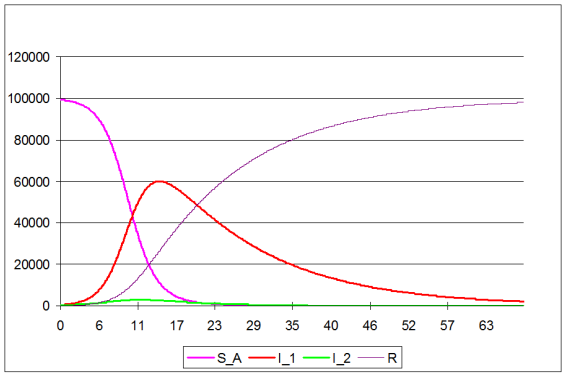

Fig. 2 SIR model without virus mutation. Red curve corresponds to infected by virus V_1, green curve corresponds to infected by virus V_1. Initial states are $I_{1_0} = 400$, $I_{2_0} = 300$, the maximum values are $I_{1\max} = 59871$, $I_{2\max} = 2968$. Epidemic peaks a reached at 15-th and 11-th days.

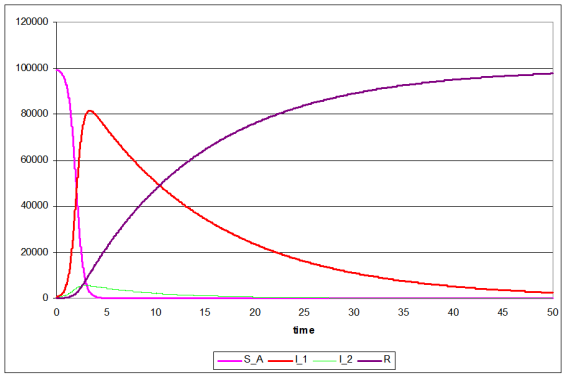

Fig. 3 SIR model with virus mutation. With the same initial states as previous figure the maximum values are $I_{1\max} = 81413$, $I_{2\max} = 2968$. Epidemic peaks a reached at 5-th and 4-th days.

In Fig. 2, we observe that for described initial states and particular case of parameters δ_i and σ_i the maximum quantity of people in the infected subpopulations is achieved at the 15-th day in group I_1, $I_{1\max} = 59871$, and at the 11-th day in the infected subpopulation I_2, maximum number of infected is $I_{2\max} = 2968$. In Fig. 3, we show the epidemic process with the same initial states for subpopulations of Susceptible, Infected and Recovered in human population together with virus mutation process. From simulation we can see that ganges in virus population lead to different epidemic behavior in human population. The maximum number of people in infected populations are $I_{1\max} = 81413$, $I_{2\max} = 5490$, reached at the 5-th and the 4-th day, respectively. We assume that virus mutation occurs according to an evolutionary process, described in Section 3. To define payoff matrix of symmetric game between different types of viruses we use next parameters of utility and energy costs b_i and C_i, here $b_1 = 100$, $b_2 = 200$, $C_1 = 400$, $C_2 = 300$, hence the corresponding stationary points (which are also Nash Equilibria) are $\{(1,0),(0,1),(\overline{x} = (0.5,0.5))\}$ (see Fig. 15).

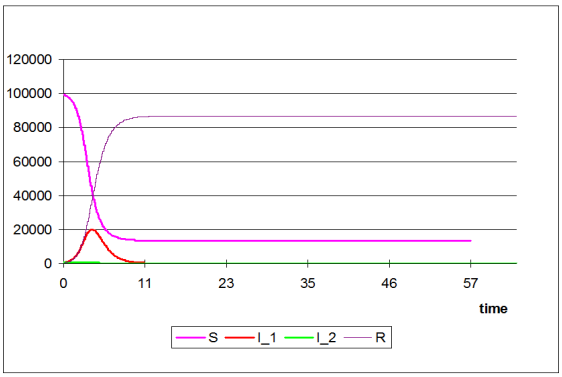

Fig. 4 SIR model with virus mutation and application of control. Functions h_i, $i = 1,2$ are concave. $h_1(u_1) = 10u_1$, $h_2(u_2) = 5u_2$. Maximal quantity of infected are $I_{1\max} = 19942$, $I_{2\max} = 609$.

Fig. 4 shows that the number of the infected has been reduced due to the application of control parameters. As we have discussed earlier, control parameters can be interpreted as insensitive medical treatment or quarantine, applied to the infected population. The maximum number of infected in epidemic peak are $I_{1\max} = 19942$, $I_{2\max} = 609$, epidemic peaks reached at the 5-th and the 4-th day, respectively.

Figs. 5-8 illustrate the results of Proposition 1, and show the optimal treatment policies for different situations: (i) simple epidemic process, and (ii) epidemic process under influence of virus mutation. Both situations are considered under concave and convex cases for the costs functions $h_i(u_i)$.

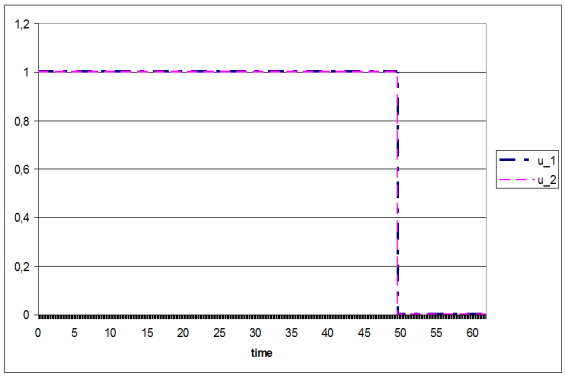

Fig. 5 Optimal control in SIR model without virus mutation, costs functions are concave h_i. Control is switched off on 50-th day. Curves for variables u_1 coincide with variable u_2.

Figs. 5 – 6 show the optimal treatment policy applied to urban population. It can be seen that the policy is active until the 50-th day and then is switched off if no influence of virus mutation process is on the human population.

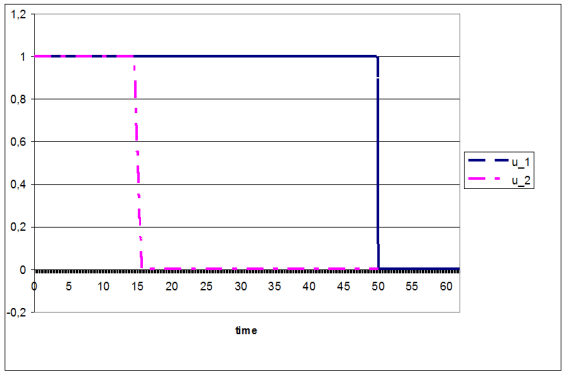

Fig. 6 Optimal control in SIR model without mutation and convex cost functions h_i, $h_1(u_1) = 20u_1^2$, $h_2(u_2) = 10u_2^2$.

Fig. 6 corresponds to the second part of Proposition **1**, under the assumption that the costs functions $h(u_i)$ are convex. In this case, the optimal control u_1 is switched off at the 50-th day, and the optimal control u_2 is switched off at the 15-th day.

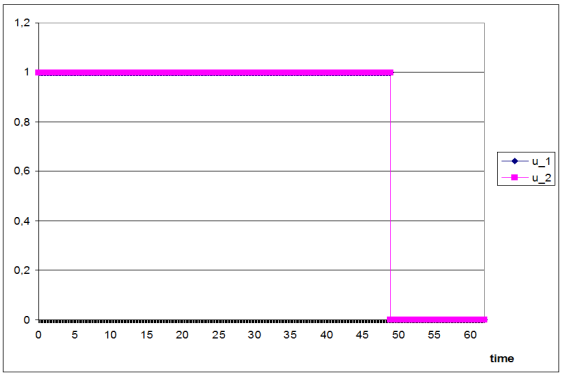

Fig. 7 Optimal control in SIR model with virus mutation and concave cost functions h_i. Control is switched of at the 48-th day for both subpopulation of infected.

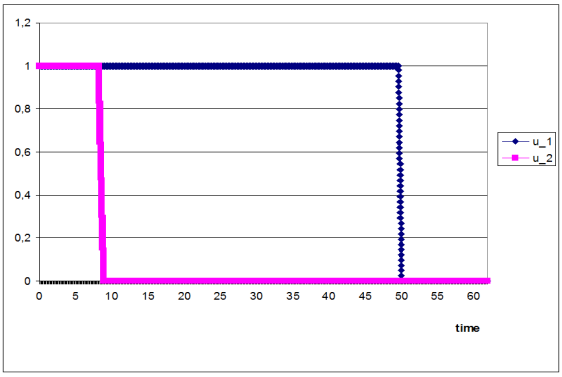

Fig. 8 Optimal control in SIR model with virus mutation and convex cost functions h_i. u_1 decays at the 9-th day, u_2 vanishes at the 50-th day.

Figs. 7 – 8 illustrate the results of Proposition 1. We take into account the impact of virus evolution on the urban population. In our model virus V_1 dominates V_2, then during the time number of infected in subpopulations I_1 is increasing, hence we need to use control parameters more intensive. In Fig. 7, we observe that the optimal controls are switched off at the 48-th day, whereas in 8 at the 9-th and the 60-th day, respectively.

Furthermore, we present a comparison between the aggregated costs as a result of the application of four different policies in our system, i.e., (i) simple SIR model without virus mutation process, (ii) simple SIR model with virus mutation process, (iii) optimal treatment policy with concave costs functions, and (iv) optimal treatment policy with convex costs functions. Next, figs. 9.–14 present the development of the aggregated costs over the time.

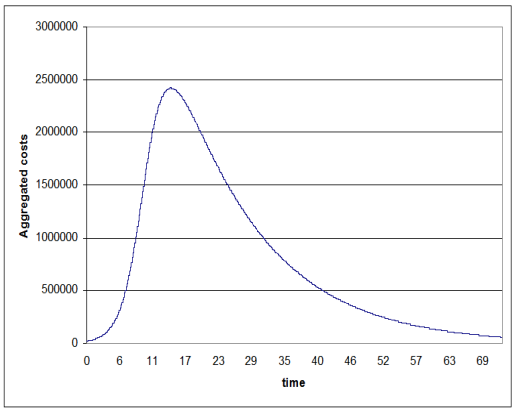

Fig. 9 Aggregated costs for SIR model without virus mutation process. Aggregated cost is $J = 4701610146$ m.u. for period of 60 days.

In Fig. 9, we show the curve associated with system costs during epidemic total epidemic duration. According to (4), we observe that aggregated cost is $J = 4701610146$ m.u. for total period. Here we do not take into account any effect from virus mutation process and application of control to human population. In this case the maximum and the minimum values are $J_{\max} = 2419518$ m.u. and $J_{\min} = 19000$ m.u. Maximum aggregate cost is reached at the 14-th day, and this time belongs to the interval between epidemic peaks corresponding to different viruses.

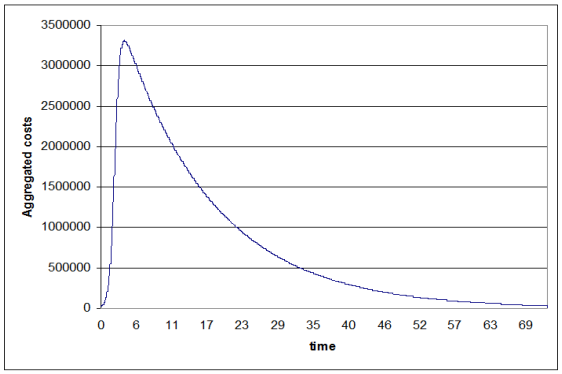

Fig. 10 Aggregated costs for SIR model, if virus mutation process occurs in human population during epidemic period. Aggregated cost is $J = 47630705$ m.u., $J_{max} = 3309432$ m.u. and $J_{min} = 19000$ m.u.

Fig. 10 illustrates aggregated costs, when epidemic process is considered together with virus mutation process. Aggregated cost is $J = 47630705$ m.u. Maximum and minimum values are $J_{max} = 3309432$ m.u. and $J_{min} = 19000$ m.u., respectively, and J reaches its maximum at the 4-th day. Here we can see that value of J is higher than in previous case, then we may assume that mutation process provoke increasing of costs for treatment in human population. Moreover, from our simulation, we see that the aggregated costs for human population increase faster when we include virus mutation process to our model, also these costs are much higher.

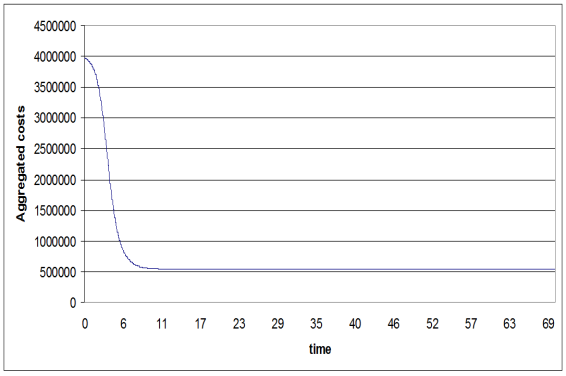

Fig. 11 Aggregated costs for SIR model under optimal control policy. Virus mutation process does not influence on the human population. Aggregated cost is $J = 4376001971$ m.u., $J_{max} = 3976008$ m.u., $J_{min} = 539541$ m.u.

Fig. 11 shows the aggregated cost in total epidemic period in human population when control is applied to the system. Here, we assume that virus mutation does not influence the human population. From the simulation, we observe that the aggregated cost is $J = 4376001971$ m.u., maximum and minimum values are $J_{max} = 3976008$ m.u., $J_{min} = 539541$ m.u. The maximum value is reached at the beginning of epidemics, and the aggregated cost decreases after the optimal control is switched on. Here, we use concave functions $h_i(u_i)$ to describe costs which are provoked by application of control. In this case, aggregated costs deeply decrease after the 6-th day, which correspond to the reduction of the infected in both subpopulations under the optimal control strategies.

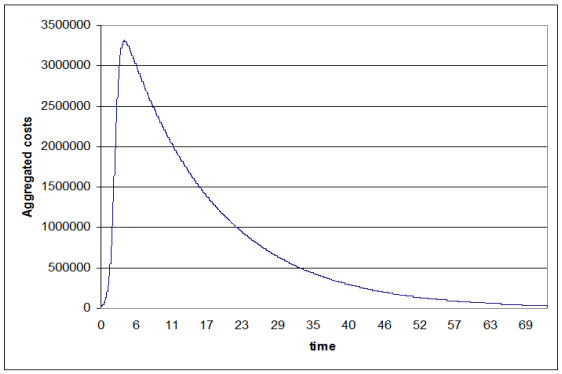

Fig. 12 Aggregated costs for SIR model with virus mutation process. Optimal control policy is applied to the system. Aggregated cost is $J = 48338102$ m.u., $J_{max} = 3309432$ m.u., $J_{min} = 19000$ m.u.

Fig. 12 shows aggregated costs for the case of convex costs functions $h_i(u_i)$, we observe that aggregated cost is $J = 48338102$ m.u., $J_{max} = 3309432$ m.u., $J_{min} = 19000$ m.u. the maximum is reached at the 4-th day instead of the 2nd day. From simulations we observe that properties of costs functions $h_i(u_i)$ perform influence to the total system costs.

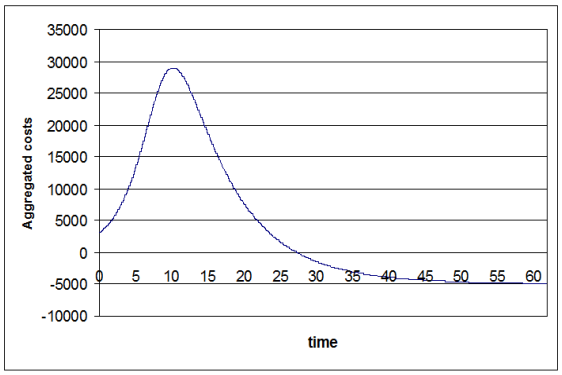

Fig. 13 Aggregated costs in SIR model without mutation process. Optimal control strategies are applied to human population, costs functions h_i are concave. Aggregated costs for total period is $J = 227204$ m.u., $J_{max} = 29011$ m.u., $J_{min} = -4887$ m.u.

In Fig. 13, we consider epidemic control without influence of virus mutations, but with the application of optimal control to the model. In this situation, the aggregated cost for total period is $J = 227204$ m.u. The maximum and minimum values are $J_{max} = 29011$ m.u., $J_{min} = -4887$ m.u., which are reached at the 11-th and the 60-th day, respectively. After the 25-th day aggregated costs become negative, thereby the income of population increases under the optimal treatment policy; i.e., the treatment costs decrease as compared with the utility from the effect of recovering.

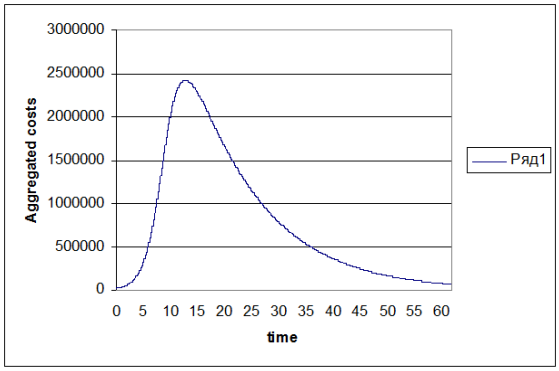

Fig. 14 Aggregated costs in SIR model without mutation process. Optimal control strategies are applied to human population, costs functions h_i are convex. Aggregated costs for total period is $J = 48284749$ m.u., $J_{\max} = 2419528$ m.u., $J_{\min} = 19121$ m.u.

Aggregated costs for SIR model without mutation process under optimal control, is $J = 48284749$ m.u. Maximum and minimum values are reached at the 13-th and the 60-th day, respectively, and $J_{\max} = 2419528$ m.u., $J_{\min} = 19121$ m.u.

Figs. 13-14 show that system aggregate costs are lower if we consider simple epidemic process, without virus mutations, and the aggregate costs increase when virus mutation occurs during the epidemic period. The influence of optimal treatment policy on the system is not as strong as the influence of mutation process.

Fig. 15 demonstrates the evolution of viruses over time in human population [21]. Here, we can see that there are three stationary states corresponding to three Nash equilibria, and that the convergence of solution trajectories of ODE (1) depends on the the initial states.

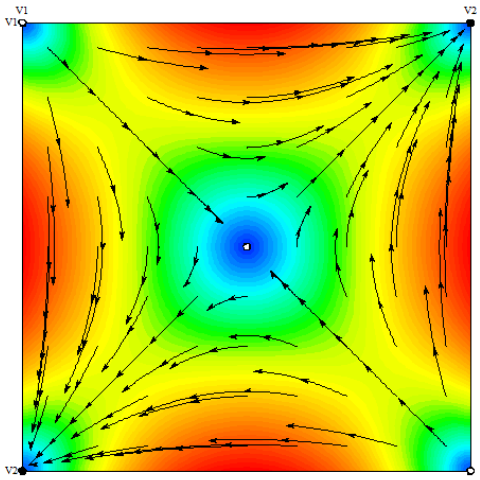

Fig. 15 Simplex of mixed strategies of the symmetric bimatrix game for modeling virus mutations. In our numerical example, the set of Nash equilibria is found to be $\{(1,0),(0,1),(0.5,0.5)\}$, where $(1,0)$, $(0,1)$ correspond to all population being V_1 and V_2, respectively; and $(0.5,0.5)$ corresponds to half of the virus being V_1 and half V_2.

From the simulation results above, we observe that the epidemic peak occurs earlier than in normal situation when the influence of virus mutation process is considered on the human population. The size of subpopulations evolves according to the virus strength or virulence of the infected, and the maximum number of the infected in the population with a stronger strain of virus is larger than its counterpart with a weak strain of virus. The population profile of the infected depends on the virus populations. We observe that the equilibria of the mutation process change under

different parameters in game payoff matrix, and hence lead to population profile of the infected. Application of control parameters, such as medical treatment or quarantine policy, allows us to reduce quantity of infected individuals in both subpopulations. However, the process of virus mutation has a significant impact on the epidemic costs under optimal control applied to the system. We observe that aggregated costs are higher when effect of virus mutation is considered in the epidemics than the cost when mutation is not included in the model. It is interesting to see that the application of optimal control does not lead to considerable reduction aggregated costs in both cases.

7 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.

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