RESEARCH ARTICLE

Mathematical modeling and optimal intervention of COVID-19 outbreak

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Background: The COVID-19 pandemic has become a formidable threat to global health and economy. The coronavirus SARS-CoV-2 that causes COVID-19 is known to spread by human-to-human transmission, and in about 40% cases, the exposed individuals are asymptomatic which makes it difficult to contain the virus.
Methods: This paper presents a modified SEIR epidemiological model and uses concepts of optimal control theory for analysis of the effects of intervention methods of the COVID19. Fundamentally the pandemic intervention problem can be viewed as a mathematical optimization problem as there are contradictory outcomes in terms of reduced infection and fatalities but with serious economic downturns.
Results: Concepts of optimal control theory have been used to determine the optimal control (intervention) levels of i) social contact mitigation and suppression, and ii) pharmaceutical intervention modalities, with minimum impacts on the economy. Numerical results show that with optimal intervention policies, there is a significant reduction in the number of infections and fatalities. The computed optimum intervention policy also provides a timeline of systematic enforcement and relaxation of stay-at-home regulations, and an estimate of the peak time and number of hospitalized critical care patients.
Conclusion: The proposed method could be used by local and state governments in planning effective strategies in combating the pandemic. The optimum intervention policy provides the necessary lead time to establish necessary field hospitals before getting overwhelmed by new patient arrivals. Our results also allow the local and state governments to relax social contact suppression guidelines in an orderly manner without triggering a second wave.

Keywords: coronavirus; COVID-19; SEIR model; epidemic model; optimization

Author summary: The global pandemic COVID-19 caused by the coronavirus SARS-CoV-2 has infected over 6 million people, resulted in over 370 thousand deaths as of May 31, 2020, and created a serious economic downturn around the world. Based on a modified SEIR model, we use the concepts from optimal control theory to determine the optimal levels of interventions, such as i) social contact mitigation and suppression and ii) pharmaceutical interventions using novel treatment modalities, for minimum impacts on the economy. Our method also determines the timeline for an orderly relaxation of social contact mitigation and suppression without triggering a second wave of infection. These results may be used as a guide by both health authorities and national governments for planning effective strategies to combat the virus outbreak.

INTRODUCTION

The global pandemic COVID-19 has challenged all countries in the world, rich and poor, powerful and powerless. As of May 31, 2020, this respiratory disease has infected over 6 million people in 188 countries causing over 370 thousand deaths. As there is no vaccine available, the COVID-19 poses a significant challenge to global health and economy, demanding a unified global effort to stop the virus. This paper investigates systematic approaches to effective intervention strategies that may be used by local and state governments and health care

facilities to minimize the impacts on human lives and livelihoods.

The coronavirus SARS-CoV-2 spreads by human-to-human transmission. Current data shows that about 20%–50% of individuals who are exposed to the virus are asymptomatic [1–3], which makes them difficult to easily identify while they keep on infecting other people through social contacts. Due to the lack of a vaccine, the scientific community is attempting to understand the epidemiological characteristics of the COVID-19 so as to develop guidelines for interventions aiming at reducing critical-care system demands and mortality. Many local and state governments have resorted to strict stay-at-home orders and shuttering of businesses to suppress the virus transmission, although there are long term economic consequences. Based on published outbreak data, Ref. [4] investigates the role of various methods of contact mitigation and suppression, such as self-quarantining, social distancing, and closure of schools and universities. Detailed reports and mathematical analyses of COVID-19 outbreaks in various countries and regions have been published in scientific media, such as [2,3,5–9] to name a few.

There are several epidemiological models available in the literature for modeling of infectious diseases [10,11], among which the SIR and SEIR models are commonly used. In the SEIR model, the population is assigned to four basic groups depending on various stages of virus infection, such as 1) Susceptible — no one is immune to the virus, 2) Exposed — individuals who carry the virus but are not infectious, 3) Infectious — individuals who need serious medical intervention, and 4) Removed — which includes individuals who have recovered or are deceased. There are many variants of the compartmental epidemiological model reported in the literature, such as [10–18], to name a few. Ref. [12] uses a combination of the SEIR model and a LSTM (long short term memory) artificial neural network to investigate the COVID-19 epidemic progression. Using the actual COVID-19 outbreak data from three provinces in China, the authors were able to predict future progression of the virus under several scenarios, such as early or late implementation of non-pharmaceutical interventions.

The COVID-19 outbreak data from various countries shows that infection and mortality rates of older population are very high compared to the younger population. Ref. [13] develops an age-specific SEIR model of virus transmission using a 5-year band within each group to age 70 and one group for age 75 and older, which provides age-specific intervention strategies for lowering the number of new infections.

It is often hypothesized that higher summer temperature and humidity might help minimize the COVID-19 virus transmission. However, based on the outbreak data from 3739 locations from around the world under varying conditions of temperature and humidity, Ref. [19] did not find any strong correlation between temperature and humidity and virus transmission. It is concluded that, if there is any, weather is more likely to play a secondary role in the control of the pandemic.

There are two possible methods of intervention for minimizing hospitalization and fatalities due to COVID-19, which are i) non-pharmaceutical intervention by mitigation and suppression of social contacts [17], and ii) pharmaceutical intervention using novel treatment modalities. Mitigation approaches of social contacts include social distancing and using face masks, etc. Contact suppression efforts include government actions by shuttering of businesses, schools and universities, and stay-at-home orders which however have long term impacts on the economy due to increased unemployment and failed businesses. Medical intervention through novel treatment modalities may help minimize the number of fatalities; however, bringing these treatment modalities to patient-care is also expensive. These conflicting outcomes may be analyzed by formulating the virus intervention problem as a mathematical optimization problem.

Optimal intervention of virus outbreaks has been considered by several researchers in the past, especially for Ebola and H1N1, and in general, for outbreaks described by SIR and SEIR models. One of the earlier works on optimal vaccination [20] was based on the SIR model. More recently, Pontryagin's minimum principle has been used in [21–23] to develop an optimal vaccination policy for Ebola. Ref. [24] uses social distancing, quarantining, and vaccination for containment of H1N1 outbreak that minimizes new infections. Optimal social distancing has been investigated for the SEIR model in [25] that minimizes new infections. Optimal control concepts have also been used in agriculture using the SIS model, such as [26]; however, a direct application of this result to human disease processes seems difficult. Ref. [27] provides a general overview of COVID19 containment by feedback from a control theoretic perspective.

The objective of this research is to develop a general mathematical framework for determining optimal intervention strategies for COVID-19 rather than characterizing or developing a containment strategy of an outbreak in any particular country or region. Our results are based on a modified SEIR model that includes virus transmission due to social contact of both infectious and exposed individuals; the latter being known to be the primary cause of COVID-19 outbreak. In addition, to facilitate the formulation of optimal control problem, we introduce a fifth compartment in the SEIR model that provides death estimate; one of the objectives of our optimization framework is minimization of fatalities. Key parameters

of this model are taken in the ballpark of those available in the open literature, such as [1–3,16,28]. We recognize that estimation of parameters of a dynamic model is, by itself, a very difficult problem, and may lead to non-unique or unreliable results [29].

We use the Pontryagin's minimum principle [30] to determine the optimum levels of two primary control strategies: i) social contact mitigation and suppression, and ii) pharmaceutical intervention using novel, albeit experimental, drugs that minimize infections, fatalities and critical care needs with minimum impacts on the economy and minimum costs of implementation of intervention strategies. Simulation results are presented to illustrate the effects of optimum intervention strategies. Our results also determine a systematic approach for relaxing mitigation and suppression guidelines without triggering a second wave of infection.

The rest of the paper is organized as follows: Section II presents a modified SEIR model for the virus progression and social interaction. Preliminary results on "flattening-the-curve" presented in Section III provide a general insight into the effects of mitigation and suppression efforts. Section IV presents the COVID-19 intervention as an optimization problem and its solution using the Pontryagin's minimum principle. Concluding remarks are discussed in Section V.

A MODIFIED SEIR MODEL

Commonly used epidemiological models that describe the progression of population through various stages of infection are SIR (Susceptible, Infectious, Removed) and SEIR (Susceptible, Exposed, Infectious, Removed) models [10,11], and their variants, for example [12–17]. In this research, we propose a modified SEIR model that includes virus transmission through social contact of exposed individuals, and frontline personnel contact with infectious individuals as depicted in Fig. 1. We also include a fifth compartment in the standard SEIR model for death estimates as one of the objectives of optimal intervention is minimization of fatalities.

In this proposed model, the progression of the population through virus infection is described in five stages: 1) Susceptible, 2) Exposed, 3) Infectious, 4) Recovered, and 5) Deceased (Fig. 1). Basically, the entire population is Susceptible to virus infection. It is known that the primary source of COVID19 virus transmission is social contact of vulnerable population with Exposed individuals, who are often asymptomatic [1]. A second source of transmission is due to frontline workers (such as, first responders, health care professionals, and law enforcement personnel) coming in direct contact with infectious individuals; however, the rate of transmission is lower than that due to Exposed individuals. Some of the Exposed individuals often recover either due to their strong natural immune system or using over-the-counter medication while others require hospitalization after a certain incubation period. Many of the Infectious individuals recover from the disease after extensive treatment, however unfortunately for some, the infection takes its toll and they are grouped as Deceased.

Denoting the population in various stages of infection as

$$x_1 = \text{Susceptible}$$

$$x_2 = \text{Exposed}$$

$$x_3 = \text{Infectious}$$

$$x_4 = \text{Recovered}$$

$$x_5 = \text{Deceased},$$

we can formally express the evolution of COVID-19 outbreak as a system of nonlinear differential equations:

$$\dot{x}_1 = -\beta_1(1-u_1)x_1 x_2/N - \beta_2(1-u_1)x_1 x_3/N$$

$$\dot{x}_2 = \beta_1(1-u_1)x_1 x_2/N + \beta_2(1-u_1)x_1 x_3/N - (\alpha + \gamma_2)x_2$$

$$\dot{x}_3 = \alpha x_2 - \gamma_1(1+u_2)x_3 - \mu x_3 \qquad (1)$$

$$\dot{x}_4 = \gamma_1(1+u_2)x_3 + \gamma_2 x_2$$
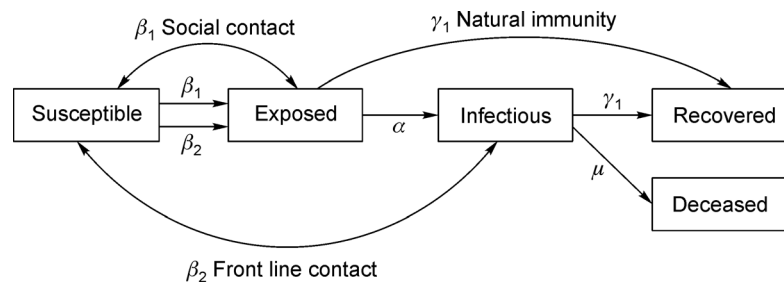
$$\dot{x}_5 = \mu x_3$$

Figure 1. Modified SEIR model of virus transmission and social interaction.

where N is the total population impacted by the outbreak. Various parameters arising in this model are:

$$\beta_1 = \text{Transmission rate due to social contact}$$

$$\beta_2 = \text{Transmission rate due to frontline contact}$$

$$\alpha = \text{Infection rate, } \alpha_1^{-1} = \text{incubation period}$$

$$\gamma_1 = \text{Recovery rate of infectious individuals,}$$

$$\gamma_1^{-1} = \text{recovery period}$$

$$\gamma_2 = \text{Immune recovery rate,}$$

$$\gamma_2^{-1} = \text{natural immune recovery period}$$

$$\mu = \text{Mortality rate.}$$

The virus outbreak can be controlled by two types of interventions: 1) mitigation and suppression of social contacts, u_1, through various measures, such as wearing face masks, social distancing [15,17], testing and quarantining, and shuttering of businesses and places of large gatherings, and 2) pharmaceutical intervention, u_2, using novel treatment modalities that minimize mortality and hospitalization period.

Suppression of social contacts can be very expensive as shuttering of businesses can have serious impacts on the economy due to loss of employment, reduction of factory production, and interruption of supply chains of food and other essential commodities. Thus we assume the constraint $0 \leqslant u_1(t) \leqslant u_{1,\max} \leqslant 1$, where $u_1 = 0$ signifies that society runs in normal mode as if there is no virus outbreak, while $u_1 = 1$ means the entire population is completely quarantined with no contact between individuals. For the pharmaceutical intervention u_2, we assume the constraint, $0 \leqslant u_2(t) \leqslant u_{2,\max}$, where $u_{2,\max}$ is determined by the efficacy of available novel treatment modalities.

It is assumed that Recovered individuals become immune to the virus so that a second infection is not possible, although this has not been scientifically proved yet. Also, for simplicity, we do not consider age-specific subgroups in various infection stages as in [13]. In addition, we have neglected natural birth and non-COVID19 related death processes although slight modifications in the equations could be made to accommodate those. Thus, the total population in the five stages remains constant, *i.e.*, $x_1(t) + x_2(t) + x_3(t) + x_4(t) + x_5(t) = N$ for all time $t \geqslant 0$.

In the above model, we have introduced a separate state variable x_5 for fatalities which is typically not found in the standard SEIR model; however, note that the fifth equation in the model (1) is actually a standalone equation that could easily be combined with the 4-th equation for Recovered, x_4, individuals. In our research, introducing x_5 as a separate state variable is required since minimization of fatalities is one of the goals of optimal intervention. We recognize that there are uncertainties in the estimation of the fatality rate μ; however other approaches, such as infection-to-death delay rule [31] based on recent COVID-19 outbreak data may provide a better estimate of the death count.

FLATTENING THE CURVE

In this section, we investigate the COVID19 outbreak under non-optimal efforts of mitigation and suppression of social contacts $u_1(t)$, implemented by various measures from social distancing and wearing face masks, to government actions, such as testing and quarantining and stay-at-home guidelines. In this section, we assume that pharmaceutical intervention $u_2(t) = 0$.

The system model (1) includes several key parameters that are unknown, which could be estimated based on an actual outbreak data. As the objective of this research is to develop a general mathematical framework for optimal intervention of epidemics, no attempts were made to estimate these key parameters; instead, these parameters were taken within the ballpark of parameters available in the open literature for COVID-19, such as [1–3,16,28]. System model parameters are usually estimated by using inverse identification or other methods, however the results are often non-unique. Non-identifiability of COVID19 model parameters has also been reported in [29]. For COVID-19, identification of model parameters is a significant challenge as there are many uncertainties, such as randomness of mobility and inaccuracy of field data of exposed individuals since many are not tested as they are often asymptomatic, and age-specific and racial differences in hospitalization of infectious patients, etc.

Statistical data shows that social contact rate of exposed individuals varies from 2 to 15 per day, incubation period varies from 2 to 14 days, the average infection period of about 7 days, and death rate is about 1% to 2.5%. For our simulation, we use the following parameters in Eq. (1): $\beta_1 = 2.5$, $\beta_2 = 0.5$, $a = 1/7$, $\gamma_1 = 1/8$, $\gamma_2 = 1/1.5$, and $\mu = 0.01$, and the population size is assumed to be $N = 100,000$. For the simulation, we consider three cases of social contact mitigation efforts: $u_1 = 0.2, 0.4, 0.6$. The simulation starts with just one Exposed individual *i.e.*, $x_2(0) = 1$, and rest of the initial states are taken as $x_1(0) = N–1$, $x_3(0) = 0$, $x_4(0) = 0$, and $x_5(0) = 0$. Figure 2 shows the simulation results for various levels of non-optimal u_1 for contact mitigation and suppression efforts.

Clearly, compared to the uncontrolled case, with increased values of u_1, there is a significant reduction in

exposed, x_2 and infectious x_3 individuals. We also observe fewer fatalities, x_5 with increased contact mitigation and suppression efforts. This figure also gives an estimate of the number of critical-care beds that would be required for treatment of patients as well as the peak time when such hospitalization may occur. This result can provide the government regulators with the valuable lead time as they prepare the health care system to receive COVID-19 patients.

Recall that simulation results presented in Fig. 2 are based on the model parameters given above and the assumed levels of contact mitigation efforts. In fact, analysis of an outbreak in any particular region is not one of the objectives of the research; however general temporal profile of our results has qualitative similarities with actual outbreaks, for example [32,33]. A better estimate of an outbreak containment time can be made only if the model parameters are identified based on field data. Nevertheless, some insights (albeit heuristic) into the outbreak containment time may be obtained from the third equation of the system model (1), which shows that overall containment time largely depends on the virus exposure, x_2 and the infectious patient recovery rate, γ_1; recall that this is a nonlinear system so that a direct correlation is not possible. In any event, as shown in Fig. 3, a longer patient recovery period leads to a prolonged virus outbreak.

OPTIMAL INTERVENTION

As discussed in the previous section, there are two types of interventions that could be used to minimize the impacts of the virus outbreak: i) mitigation and suppression of social contacts, u_1, which reduces new infections and hospitalization, and ii) pharmaceutical intervention u_2 which reduces fatalities and increases recovery. However, the intervention u_1 can be economically very expensive due to loss of employment and reduction of business activities. Likewise, pharmaceutical intervention u_2 depends on the availability of antiviral treatment techniques, albeit experimental, and could also be expensive. Thus, the COVID-19 intervention problem could be formulated as a mathematical optimization problem with the goal of minimizing infections and fatalities with minimum impacts on the economy and costs of implementation.

Formally, this optimization problem can be stated as follows:

$$\min_{\{u_1, u_2\}} J(u_1, u_2) = \frac{1}{2}\int_0^T \{q_2 x_2^2 + q_3 x_3^2 - q_4 x_4^2 + q_5 x_5^2\}\,\mathrm{d}t$$

$$+ \frac{1}{2}\int_0^T \{r_1 u_1^2 + r_2 u_2^2\}\,\mathrm{d}t, \qquad (2)$$
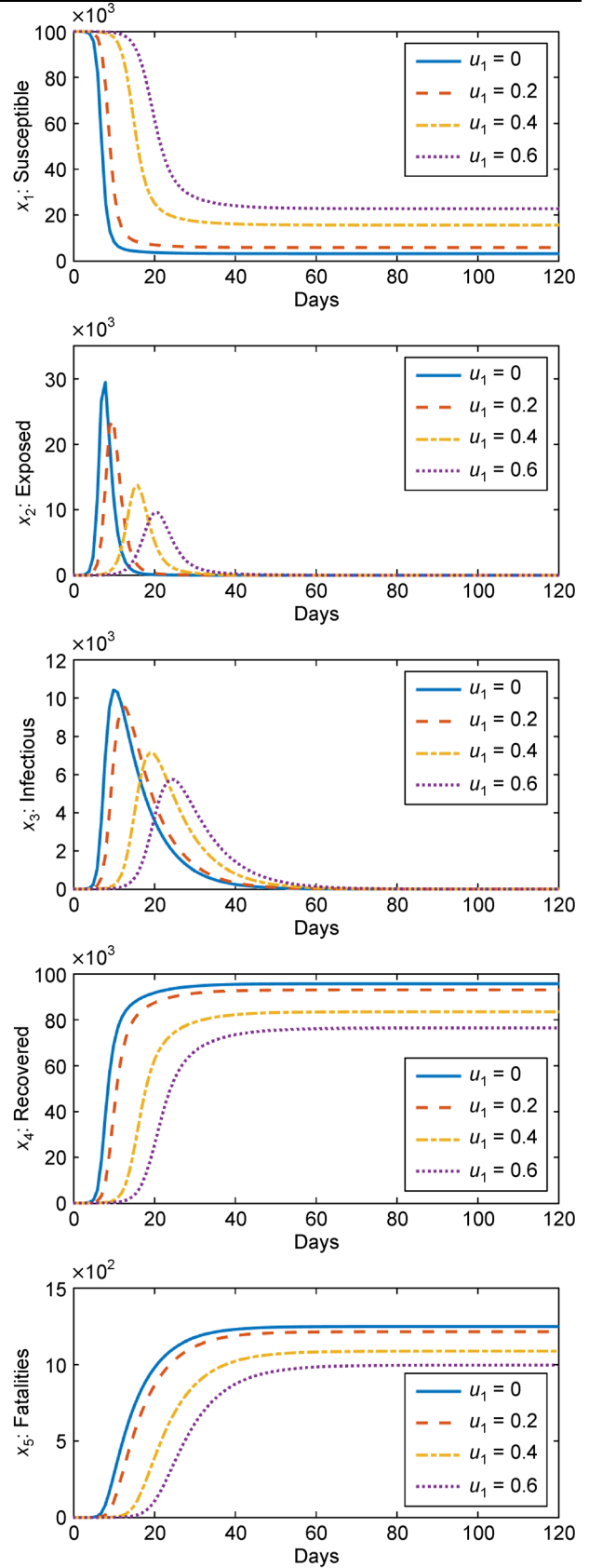
subject to the constraints:

Figure 2. COVID-19 outbreak profile for various levels of contact mitigation and suppression u_1.
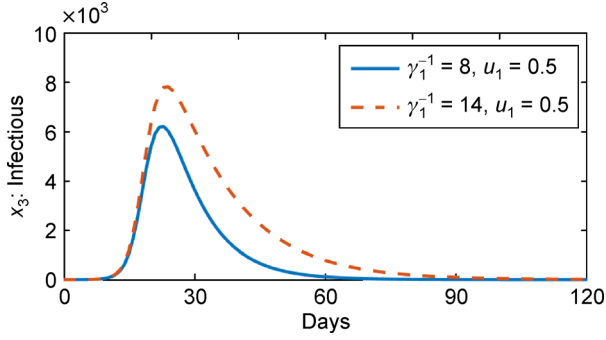
Figure 3. Reduction of outbreak containment time with reduced patient recovery period (r_1^{-1}).

$$0 \leqslant u_1(t) \leqslant u_{1,\max} \leqslant 1, \ 0 \leqslant u_2(t) \leqslant u_{2,\max}$$

and the dynamic constraint, Eq. (1), where q_2, q_3, q_4, and q_5 are the weights on the state variables based on their relative importance. Here the first two terms in the cost function are intended to minimize the number of Exposed x_2 and Infectious x_3 individuals, while the third term maximizes the number of Recovered x_4 individuals. The fourth term in the cost function minimizes the number of deaths x_5 due to infection. The second integral in the cost function represents the cost of control with the weights r_1 and r_2 representing their relative expenses. Note also that a high weight r_1 signifies high economic impact due to contact mitigation and suppression efforts. Likewise, a high weight r_2 reflects high cost of novel treatment modalities.

The solution of the optimization problem (2) can be obtained using the Pontryagin's minimum principle [30]. Denote the state vector by $\mathbf{x}(t) \in \mathcal{R}^5$ and the control vector $\mathbf{u}(t) \in \mathcal{R}^2$. Then the optimization problem can be formally stated as

$$\min_{\mathbf{u}} J(\mathbf{u}) = \frac{1}{2} \int_0^T L(\mathbf{x},\mathbf{u}) \mathrm{d}t,$$

as in Eq. (2) subject to the system dynamics Eq. (1) denoted as

$$\dot{\mathbf{x}} = f(\mathbf{x},\mathbf{u})$$

$$\mathbf{x}(0) = \mathbf{x}_0, \tag{3}$$

with the controls taking values from the admissible set

$$\mathcal{U} = \{\mathbf{u} = \{u_1, u_2\} : 0 \leqslant u_1(t) \leqslant u_{1,\max} \leqslant 1, 0 \leqslant u_2(t) \leqslant u_{2,\max}\}. \tag{4}$$

To find the optimum solution, define the Hamiltonian as

$$H(\mathbf{x},\psi,\mathbf{u}) = L(\mathbf{x},\mathbf{u}) + \psi^T f(\mathbf{x},\mathbf{u}). \tag{5}$$

Then according to the Pontryagin's minimum principle,

the optimum solution minimizes the Hamiltonian

$$H(\mathbf{x},\psi,\mathbf{u}) \leqslant H(\mathbf{x},\psi,\mathbf{v}) \text{ for all } t \in [0,T],$$

for all admissible controls $\mathbf{v} \in \mathcal{U}$, where the adjoint variable $\psi(t) \in \mathcal{R}^5$ satisfies

$$\begin{cases} \dot{\psi} = \dfrac{\partial H}{\partial \mathbf{x}} = \dfrac{\partial L}{\partial \mathbf{x}} - \left[\dfrac{\partial f}{\partial \mathbf{x}}\right]^T \psi \\ \psi(T) = 0 \end{cases} \tag{6}$$

All equations for the necessary conditions of optimality stated above could be easily derived using the system model (1) and the cost function (2). We skip the details here for brevity.

For simulation, the following weights were used in the cost function: $q_2 = q_3 = 10^{-4}$, $q_4 = 10^{-8}$, and $q_5 = 10^{-3}$. Note that we must use small weights in the cost function (2) since the system model (1) is not normalized with respect to the population size. For the control weights, we choose $r_1 = 50$ and $r_2 = 1$ signifying that contact mitigation and suppression efforts can be very expensive as it has significant impact on the economy. As for the control limits, we assume that $u_{1,\max} = 0.5$ which represents a moderate level of government action on reducing social contacts. For the medical intervention bound, we choose $u_{2,\max} = 0.2$, which corresponds to 20% improvement in patient recovery rate. A recent clinical study [34] reported about 25% reduction in patient recovery period by using a common anti-viral drug on severely infected patients.

Clearly, as shown in Fig. 4, optimal contact mitigation and suppression, u_1 helps contain the spread of infection and minimize fatalities. The number of fatalities could be further decreased by pharmaceutical intervention u_2 which however does not have any significant impact on initial virus exposure so that x_2 and x_3 populations are almost the same as for both cases as seen in Fig. 4. This is expected since u_2 is applicable to hospitalized patients only. In these figures, u_1 and u_2 "optimal" refer to optimal control policies as shown in Fig. 5.

Figure 5 shows the optimal control policies u_1 and u_2 as a function of time for the two optimization scenarios. The first panel (of Fig. 5) for the optimal u_1 shows that mitigation and suppression of social contacts does not have to be prolonged for too long, and could rather be relaxed in an orderly manner without triggering a second wave. Application of pharmaceutical intervention u_2 helps relaxing the suppression efforts even faster. These results would assist state and local administrators in making their policy decisions on implementing or relaxing social contact mitigation and suppression efforts. The first panel of Fig. 5 for u_1 offers a timeline for an orderly withdrawal of stay-at-orders and other suppression activities without triggering a second wave. Use of
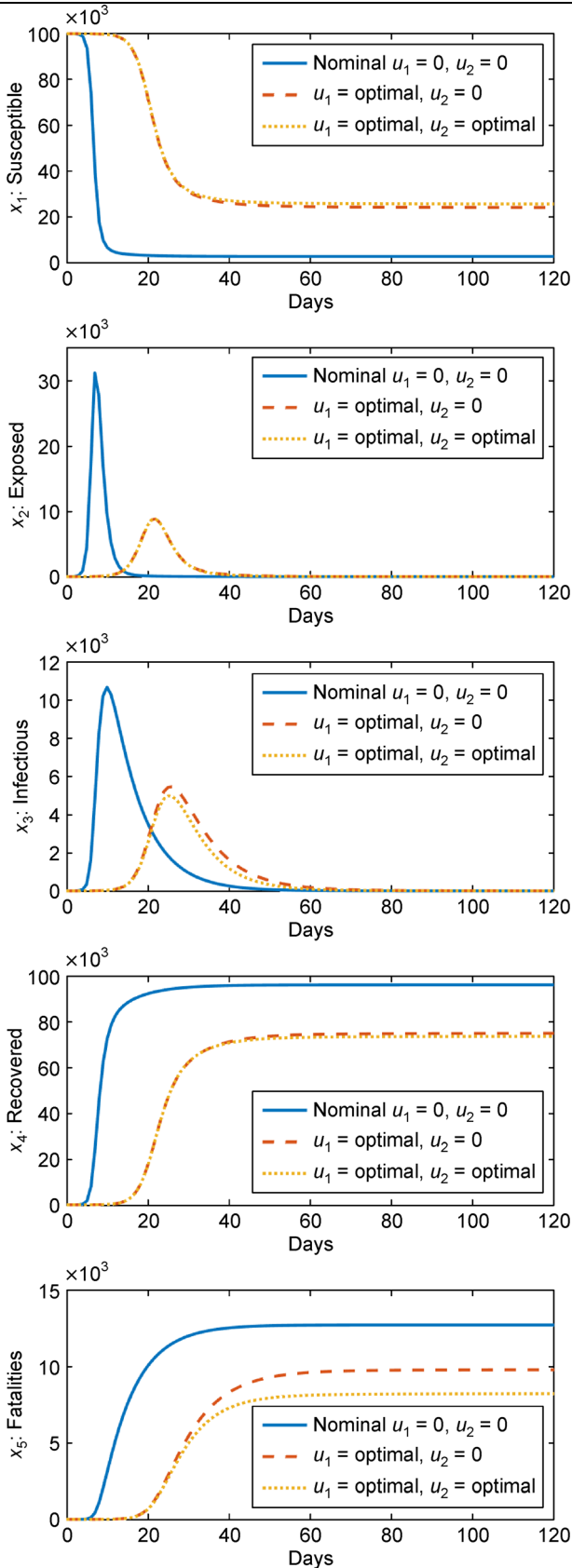
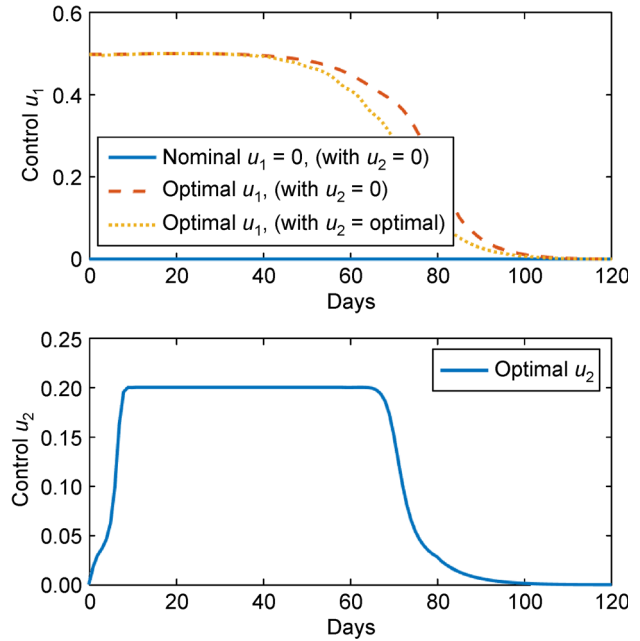Figure 4. Comparison of the optimal solution with the nominal response.

Figure 5. Optimal intervention policies corresponding to state trajectories shown in Fig 4.

pharmaceutical intervention u_2 helps relaxing the stay-at-orders even faster. The second panel of Fig. 5 shows pharmaceutical intervention u_2 over the study period. State trajectories corresponding to these controls are shown in Fig. 4.

CONCLUSIONS

In this paper, we propose a modified SEIR model for the COVID-19 pandemic and use optimal control concepts to minimize the impacts on human lives and their livelihoods. For containment of the outbreak, two methods of intervention are considered: i) contact mitigation and suppression, and ii) pharmaceutical intervention using novel treatment modalities, which have contradicting outcomes of minimizing infections and fatalities vs loss of employment and economic activities. Because of these contradicting outcomes, the virus intervention problem could be viewed as a mathematical optimization problem, and solved using concepts from optimal control, such as the Pontryagin's minimum principle. Our results provide a systematic approach to determining optimum levels of intervention actions that may be used by the state and local governments in their efforts to contain the outbreak. Our results also provide a systematic and orderly approach of relaxing stay-at-home orders without triggering a second wave of infection.

It should be noted that our results provide a general mathematical framework for the development of containment efforts for a virus outbreak, which is based on a

modified SEIR model with several unknown parameters. The first step in this process includes the determination of these parameters using an actual outbreak data and an inverse identification method or other approaches.

As the world community is frantically engaged in research trying to find a vaccine, it is absolutely necessary to stop the spread of the virus, save lives, and minimize miseries inflicted on millions of families, which demands a unified and global collaboration. We believe that the results of this paper may be useful as a guide to both health care authorities and national and local governments for planning effective strategies to fight such deadly viruses as COVID-19 in the future.

COMPLIANCE WITH ETHICS GUIDELINES

The authors Saroj K Biswas and Nasir U Ahmed declare that they have no conflict of interests.

All procedures performed in this research were in accordance with the ethical standards of their institutions, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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