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Optimal Control of An Infectious Disease Model In Case of Imperfect Testing

Tuğba AKMAN[1], Rana ESEN[2] and Fikriye YILMAZ[3]

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Research Article

Corresponding Author
Fikriye YILMAZ
fnozdemir@gazi.edu.tr

ORCID of the Authors
T.A: 0000-0003-1206-2287
R.E: 0000-0003-4423-7491
F.Y: 0000-0003-0002-9201

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Abstract

In this work, we study the spread of a communicable disease using an SIR model that includes the effect of imperfect testing. The model is extended by adding birth and natural death rates, and it uses a standard incidence rate to describe disease dynamics over a long period, rather than just during an outbreak. We find the disease-free equilibrium and the basic reproduction number to analyze the system's stability. To control transmission and testing rates, we set up an optimal control problem to find the best values. To do this, we simulate three different control problems: one with only isolation, one with only testing, and one with both. We see that reducing contact between susceptible and infected people is very important, along with having an effective testing strategy.

Keywords: Mathematical modeling, optimal control problem, reproduction number, stability analysis, testing

Kusurlu Test Durumunda Bulaşıcı Hastalık Modellerinin Optimal Kontrolü

[1]University of Turkish Aeronautical Association, Department of Computer Engineering, Ankara, Türkiye

[2]Gazi University, Graduate School of Natural and Applied Sciences, Ankara, Türkiye

[3]Gazi University, Faculty of Science, Department of Mathematics, Ankara, Türkiye

Öz

Bu çalışmada, bulaşıcı bir hastalığın yayılımını kusurlu testlerin etkisini içeren bir SIR modeli kullanarak inceliyoruz. Model, doğum ve doğal ölüm oranları eklenerek genişletilmiş ve sadece bir salgın dönemi için değil, uzun bir zaman aralığında hastalık dinamiklerini tanımlamak amacıyla standart bulaşma oranı kullanılmıştır. Hastalığın olmadığı denge noktasını ve temel üreme sayısını sistemin kararlılığını analiz etmek için buluyoruz. Bulaşma ve test oranlarını kontrol etmek için en uygun değerleri bulmaya yönelik bir optimal kontrol problemi kurduk. Bunu yapmak için üç farklı kontrol problemi simülasyonu yapıyoruz: yalnızca izolasyon uygulanan, yalnızca test oranının optimize edildiği ve her iki müdahalenin birlikte uygulandığı durumlar. Duyarlı ve enfekte bireyler arasındaki temasın azaltılmasının, etkili bir test stratejisiyle birlikte, oldukça önemli olduğunu gözlemledik.

Anahtar Kelimeler: Matematiksel modelleme, optimal kontrol problemi, temel üreme sayısı, kararlılık analizi, test

Introduction

Mathematical models of Kermack and McKendrick led to the formation of the field of Mathematical Epidemiology [1]. Since then, mathematical modeling of infectious diseases has been a powerful tool to express communicable diseases in a hypothetical manner, and conditions to eliminate the disease have been analyzed based on these models [2]. Public health officials in the United States have focused on the control and eradication of organisms causing infectious diseases by founding the hospital discipline of infection control against the nosocomial epidemic in 1950s [3]. In the twenty-first century, several epidemics were faced with and improved sanitation, vaccination and access to health care have made positive contributions to the eradication or control of infectious diseases [4, 5].

Intervention strategies such as quarantine, vaccination and treatment are often necessary to eradicate the disease or to control its spread, and if these strategies are not implemented in a timely manner and adequately, disease eradication will be impossible. In contrast, the optimal control strategies can be investigated via mathematical models [6]. For example, Berge et al. constructed an Ebola model by incorporating imperfect contact tracing, isolation and hospitalization, and they discovered that combination of high contact tracing and effective isolation is the optimal intervention [7]. Nyerere et al. investigated the optimal control of Typhoid fever and they found out that both vaccination for susceptible individuals and the screening and treatment of asymptomatic infected individuals were crucial to reduce the spread [8]. Teytsa et al. considered cholera as bacterial-borne diseases via a within-host model and release of lytic vibriophages was found to be the optimal choice to eliminate bacteria [9]. Gao and Huang interpreted tuberculosis dynamics with a new model and applied vaccination and treatment [10]. Zaman et al. investigated the optimal vaccination strategy for a smoking model [11]. Akman developed a model for tuberculosis by comparing treatment at home and in hospital via an optimal control problem (OCP) [12]. Omame et al. constructed a co-infection model for Chlamydia trachomatis and human papillomavirus, and they concluded that prevention from both viruses was the most successful strategy [13]. Rabiu et al. proposed an HIV/AIDS-resistant model [14], and they discovered that combination of positive behavior change, a balanced diet and antiretroviral treatment is the optimal intervention to guarantee disease eradication. Akman investigated an OCP for a tuberculosis model and a waterborne pathogen model to eliminate the disease in the community via non-integer order models [15, 16]. Eikenberry et al. examined the impact of face masks during the COVID-19 pandemic and found that face mask use was effective in reducing the transmission of disease [17]. Lemos-Paiao et al. established a COVID-19 model with a Portuguese case study and the basic reproduction number that the authors found was compatible with the one found by public authorities [18]. Akman et al. developed a model for the early dynamics of COVID-19 in Turkey and investigated the effect of underreporting to the peak of the spread [19]. Chhetri studied a within-host model for COVID-19 by focusing on optimal drug regimen for four drugs with the aim of helping physicians in their clinical decision to treat COVID-19 patients [20].

As another point of view, the study of Villela can be mentioned where effect of imperfect testing has been considered as a factor in disease dynamics [21]. In that work, the population is split into susceptible, infected, and recovered subgroups and effect of false positive tests is considered. The model, unlike the classical SIR model, includes two more compartments, namely $\hat{S}$ and $\hat{I}$, to denote the number of susceptible and infected individuals who are tested positive, respectively. Motivated from the study [21], we firstly propose a mathematical model. We prove that the solution is positive and bounded provided

that the initial conditions are non-negative. Then, we obtain the disease-free equilibrium (DFE) point, and find the basic reproduction number R_0 based on the next generation matrix (NGM), and discuss the stability of the DFE [22]. We secondly construct an OCP for planning quarantine/isolation and optimizing the test rate to minimize the number of infected individuals. We provide the optimality system and explain the details of the forward-backward sweep (FBS) algorithm [23] which is used to solve the OCP numerically. We then illustrate the success of the interventions with some simulation results. The rest of the paper is organized as follows: In the first section, we develop the mathematical model, and prove that the solution is positive and bounded. In the second section, the DFE point is found and its stability is analyzed. In the third section, the OCP is formalized with three interventions and optimality system is written as a theorem. Some numerical results are presented in the section of simulation results. Finally, the paper ends with a summary and conclusion.

Mathematical Model

In this paper, Villela's model [21] is modified to interpret the long-term dynamics of an infectious disease so that the population size does not remain constant. The model is constructed by splitting the total population at time t, denoted $N := N(t)$, into five mutually exclusive subgroups. The model variables are defined as $S := S(t)$ (susceptible individuals), $\hat{S} := \hat{S}(t)$ (susceptible individuals but deemed infected), $I := I(t)$ (infected individuals), $\hat{I} := \hat{I}(t)$ (infected individuals who are tested–positive) and $R := R(t)$ (recovered individuals). Recruitment of susceptible individuals, such as birth, occur at the rate of Σ. Susceptible individuals in S and $\hat{S}$ get infected at the rates of β and $\hat{\beta}$, respectively. Susceptible individuals tested, and they are misclassified as infected at the rate of c. The term $I + k\hat{I}$ represents the number of individuals who become sick as a result of interaction of infected individuals with susceptible individuals at a rate of β, whereas the parameter k denotes the self protection rate of infected individuals who tested positive. Misclassified susceptible individuals are tested again and move to the susceptible subgroup at the rate of d, if the test is negative. Infected and tested individuals move to the compartment $\hat{I}$ at the rate of θ if the test result is positive. Infected individuals who are tested and not tested recover at the rates of γ and $\hat{\gamma}$, respectively. All individuals die at the rate of μ for simplicity. With these assumptions, we propose the following model:

$$
\begin{aligned}
\frac{dS}{dt} &= \Sigma - cS - \beta\frac{S(I+k\hat{I})}{N} - \mu S + d\hat{S},\\
\frac{d\hat{S}}{dt} &= cS - \hat{\beta}\frac{\hat{S}(I+k\hat{I})}{N} - (\mu+d)\hat{S},\\
\frac{dI}{dt} &= \beta\frac{S(I+k\hat{I})}{N} + \hat{\beta}\frac{\hat{S}(I+k\hat{I})}{N} - (\theta+\gamma+\mu)I,\\
\frac{d\hat{I}}{dt} &= \theta I - \hat{\gamma}\hat{I} - \mu\hat{I},\\
\frac{dR}{dt} &= \hat{\gamma}\hat{I} + \gamma I - \mu R,\\
S(0) = S_0, \hat{S}(0) &= \hat{S}_0, I(0) = I_0, \hat{I}(0) = I_0, R(0) = R_0,
\end{aligned}
\tag{1}
$$

with the non-negative values of initial subgroups $S_0, \hat{S}_0, I_0, \hat{I}_0, R_0$, with $N = S + \hat{S} + I + \hat{I} + R$.

We show that the solution to Eq. (1) is positive and bounded.

Theorem 1. A solution $(S(t), \hat{S}(t), I(t), \hat{I}(t), R(t))$ of the system (1) with non-negative initial conditions is positive and bounded on $[0, \infty)$.

Proof. Let $(S_0, \hat{S}_0, I_0, \hat{I}_0, R_0)$ be non-negative values for the model variables in Eq. (1). Firstly, let us assume that the variable S is not positive for some value a in the interval $[0, T]$ with $T > 0$. Since the initial value of S is positive, there is a value $t_1 < a$ such that $S(t_1) = 0$ and then $S(a) < 0$. Now, $S(t) > 0$ in the interval $[0, t_1)$. Since $c > 0$, it follows that

$$\frac{d\hat{S}}{dt} = cS - \hat{\beta}\frac{\hat{S}(I + k\hat{I})}{N} - (\mu + d)\hat{S} \geq -\left(\hat{\beta}\frac{(I + k\hat{I})}{N} + (\mu + d)\right)\hat{S}.$$

Separation of variables implies that,

$$\frac{d\hat{S}}{\hat{S}} \geq -\left(\hat{\beta}\frac{(I + k\hat{I})}{N} + (\mu + d)\right)dt.$$

Then, we get

$$\hat{S}(t) \geq \hat{S}(0)\exp\left(-\int_0^t [\hat{\beta}\frac{(I(u) + k\hat{I}(u))}{N} + (\mu + d)]du\right) > 0.$$

This shows that $\hat{S}(t) > 0$ in the interval $[0, t_1)$. Now, we consider

$$\frac{dS}{dt} = \Sigma - cS - \beta\frac{S(I + k\hat{I})}{N} - \mu S + d\hat{S}.$$

Since $\hat{S} > 0, \Sigma > 0$; the following inequality holds for all $t \in [0, t_1]$:

$$\frac{dS}{dt} \geq -\left(c - \beta\frac{(I + k\hat{I})}{N} - \mu\right)S.$$

Then, for $t = t_1$, we get

$$S(t_1) \geq S(0)\exp\left(-\int_0^{t_1}\left[\beta\frac{(I(u) + k\hat{I}(u))}{N} + (c + \mu)\right]du\right) > 0,$$

which is a contradiction to the assumption $S(t_1) = 0$. Thus, $S(t) \geq 0$ for all $t \in [0, T]$. Then, $\hat{S} \geq 0$ for all $t \in [0, T]$.
Moreover, the above argument can be used to show $I \geq 0$ and $\hat{I} \geq 0$. Firstly, I is assumed to be negative, then we get a contradiction by using the equations for $\frac{dI}{dt}$ and $\frac{d\hat{I}}{dt}$. For the last variable R, we get

$R(t) \geq S(0)\exp(-\mu t) > 0.$

In addition, we consider the total population N and we add all equations in the Eq. (1) up to obtain

$$\begin{aligned}\frac{d(S+\hat{S}+I+\hat{I}+R)}{dt} &= \Sigma - \mu(S+\hat{S}+I+\hat{I}+R),\\ &\Rightarrow \frac{dN}{dt} = \Sigma - \mu N,\\ &\Rightarrow \frac{dN}{dt} + \mu N = \Sigma,\\ &\Rightarrow N(t) = \frac{\Sigma}{\mu} + K\exp(-\mu t), \text{ for a constant } K,\\ &\Rightarrow N(t) = \frac{\Sigma}{\mu} + \left(N(0) - \frac{\Sigma}{\mu}\right)\exp(-\mu t).\end{aligned}$$

We observe that as $t \to \infty$, $N \to \frac{\Sigma}{\mu}$. Therefore, $S, \hat{S}, I, \hat{I}$ and R are bounded, which completes the proof.

We note that all partial derivatives of the right-hand side of Eq. (1) are dependent on the model variables and constants, so their derivatives are bounded which gives the existence and uniqueness of the solution from the standard theory of SEIR models. In the next section, we present the stability analysis by obtaining the DFE and R_0.

Stability Analysis

If $R_0 > 1$, then an infectious individual leads, on average, more than one individual to be infected. Otherwise, disease is eliminated [2]. Here, we use the method of the NGM by following the work [22] to derive R_0.

Suppose that there are l infected segments and k uninfected segments. Therefore, an ordinary differential equation has $k+l$ dependent variables. Let x and y be the vectors of dependent variables in the infected and uninfected compartments, respectively; so, $x \in \mathbb{R}^l$ and $y \in \mathbb{R}^k$. The system of differential equations is defined as:

$$x_i' = f_i(x,y), i = 1,2,\ldots,l, \quad y_i' = h_j(x,y), j = 1,2,\ldots,k. \tag{2}$$

The right side of the infected compartment is divided as follows:

$$\begin{aligned}x_i' &= \tilde{F}_i(x,y) - \tilde{V}_i(x,y)\,, \quad i = 1,2,\ldots,l,\\ y_j' &= h_j(x,y), \qquad\qquad\quad j = 1,2,\ldots,k.\end{aligned} \tag{3}$$

Here,

- $\tilde{\mathcal{F}}_i(x,y)$ represents new infections occurring in state i,
- $\tilde{\mathcal{V}}_i(x,y)$ represents the remaining part in the model.

Firstly, we find the DFE point $\tilde{P}_\circ$ of Eq. (1) as

$$\tilde{P}_\circ = (S_\circ, \hat{S}_\circ, I_\circ, \hat{I}_\circ, R_\circ) = \left(\frac{\Sigma(\mu+d)}{\mu(c+\mu+d)}, \frac{\Sigma c}{\mu(c+\mu+d)}, 0, 0, 0\right).$$

By following the idea of the NGM [22], we obtain

$$\tilde{F} = \begin{bmatrix} \dfrac{\beta S(I+k\hat{I})}{N} + \dfrac{\hat{\beta}\hat{S}(I+k\hat{I})}{N} \\ \\ 0 \end{bmatrix}, \quad \tilde{V} = \begin{bmatrix} (\theta+\gamma+\mu)I \\ \\ -\theta I + (\hat{\gamma}+\mu)\hat{I} \end{bmatrix}.$$

Their Jacobian matrices evaluated at the DFE point $\tilde{P}_\circ$ are found as

$$F = \frac{1}{\mu+d+c}\begin{bmatrix} \beta(\mu+d)+c\hat{\beta} & k(\beta(\mu+d)+c\hat{\beta}) \\ \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \theta+\gamma+\mu & 0 \\ -\theta & \hat{\gamma}+\mu \end{bmatrix}.$$

Then, we obtain the matrix

$$FV^{-1} = \frac{1}{(\mu+d+c)(\hat{\gamma}+\mu)(\theta+\gamma+\mu)}\begin{bmatrix} (\beta(\mu+d)+c\hat{\beta})(\hat{\gamma}+\mu+k\theta)) & k(\beta(\mu+d)+c\hat{\beta})(\theta+\gamma+\mu)) \\ 0 & 0 \end{bmatrix}.$$

The largest eigenvalue of the matrix FV^{-1}, which is R_0, is obtained as

$$R_0 = \rho(FV^{-1}) = \left(1+\frac{k\theta}{\hat{\gamma}+\mu}\right)\frac{\beta(\mu+d)+c\hat{\beta}}{(\theta+\gamma+\mu)(d+\mu+c)}, \tag{4}$$

where ρ denotes the spectral radius [22]. Finally, the stability result is established in the following theorem and the proof is given in the Appendix:

Theorem 2. The DFE point $\tilde{P}_\circ = (S_\circ, \hat{S}_\circ, I_\circ, \hat{I}_\circ, R_\circ)$ is locally asymptotically stable, if $R_0 < 1$.

In addition, we investigate the connection between R_0 in Eq. (4) and its counterpart for a SIR model, as done in [21]. Villela defines $\theta = r\psi$ and $c = r(1-\epsilon)$ where r is the testing rate, ψ is the test sensitivity and ϵ is the test specificity [21]. If we rewrite R_0 by inserting θ and c, then we get the expression

$$R_0 = \frac{(\hat{\gamma}+\mu+kr\psi)(\beta(\mu+d)+\hat{\beta}r(1-\epsilon))}{(r\psi+\gamma+\mu)(\mu+d+r(1-\epsilon))(\hat{\gamma}+\mu)}.$$

We observe that

$$\lim_{r\to\infty} R_0 = \frac{k\hat{\beta}}{\hat{\gamma}+\mu}.$$

Indeed, this expression is R_0 of a SIR model with the infection rate $\hat{\beta}$ and the recovery rate $\hat{\gamma}$ [24]. A similar discussion can be found for the original model in Villela's study as well [21].

Optimal Control Problem

Optimal control theory has proven to be a highly successful tool to simulate response strategies. In order to prevent the spread of disease, high rates of testing and strict quarantine/isolation of susceptible individuals (S and $\hat{S}$) and those who have the capacity to transmit the disease (I and $\hat{I}$) are required.
In this current study, we incorporate the tools of optimal control theory to minimize the number of infected individuals together with the cost of implementing the intervention strategies. Here, we construct three OCPs for quarantine/isolation, for optimal testing and combination of these strategies. Our aim is to find an optimal control strategy on a prespecified time interval $[0, T]$ for $T > 0$. Since investigation of the optimal testing is one of our goals, we explicitly interpret the testing rate by substituting $\theta = r\psi$ and $c = r(1-\epsilon)$ into Eq. (1).
We define the set of admissible controls as

$$\begin{aligned} U = \{&u_1(t), u_2(t), u_3(t) : u_1(t), u_2(t), u_3(t) \text{ are measurable,} \\ &0 \leqslant u_1(t), u_2(t) \leqslant M_1, 0 \leqslant u_3(t) \leqslant M_2, \quad t \in [0,T]\}, \end{aligned} \tag{5}$$

and define the OCP on U as

$$J[(u_1(t), u_2(t), u_3(t))] = \int_0^T \big(I(t) + \hat{I}(t) + \frac{w_1}{2}u_1^2 + \frac{w_2}{2}u_2^2 + \frac{w_3}{2}u_3^2\big)dt, \tag{6}$$

subject to

$$\begin{aligned} \frac{dS}{dt} &= -u_3(t)(1-\epsilon)S - (1-u_1(t))\beta\frac{S(I+k\hat{I})}{N} - \mu S + d\hat{S} + \Sigma, \\ \frac{d\hat{S}}{dt} &= u_3(t)(1-\epsilon)S - (1-u_2(t))\hat{\beta}\frac{\hat{S}(I+k\hat{I})}{N} - (\mu+d)\hat{S}, \\ \frac{dI}{dt} &= (1-u_1(t))\beta\frac{S(I+k\hat{I})}{N} + (1-u_2(t))\hat{\beta}\frac{\hat{S}(I+k\hat{I})}{N} - (u_3(t)\psi + \gamma + \mu)I, \\ \frac{d\hat{I}}{dt} &= u_3(t)\psi I - \hat{\gamma}\hat{I} - \mu\hat{I}, \\ \frac{dR}{dt} &= \hat{\gamma}\hat{I} + \gamma I - \mu R, \\ S(0) = S_0, \hat{S}(0) &= \hat{S}_0, I(0) = I_0, \hat{I}(0) = I_0, R(0) = R_0, \end{aligned} \tag{7}$$

with the non-negative initial conditions and the weight constants ω_1, ω_2 and ω_3. The goal is to determine the control function $(u_1^*(t), u_2^*(t), u_3^*(t)) \in U$ satisfying

$$J[(u_1^*(t), u_2^*(t), u_3^*(t))] = \min_{(u_1(t),u_2(t),u_3(t))\in U} J[(u_1(t), u_2(t), u_3(t))].$$

This problem is solved using the optimality system and it requires the Hamiltonian which is written as

$$\begin{aligned}
H &= H(S(t), \hat{S}(t), I(t), \hat{I}(t), R(t), u_1(t), u_2(t), u_3(t)) \\
&= I(t) + \hat{I}(t) + \frac{w_1}{2}u_1^2(t) + \frac{w_2}{2}u_2^2(t) + \frac{w_3}{2}u_3^2(t) \\
&+ \lambda_1(t)\bigg(- u_3(t)(1-\epsilon)S - (1-u_1(t))\beta\frac{S(I+k\hat{I})}{N} - \mu S + d\hat{S} + \Sigma\bigg) \\
&+ \lambda_2(t)\bigg(u_3(t)(1-\epsilon)S - (1-u_2(t))\hat{\beta}\frac{\hat{S}(I+k\hat{I})}{N} - (\mu+d)\hat{S}\bigg) \\
&+ \lambda_3(t)\bigg((1-u_1(t))\beta\frac{S(I+k\hat{I})}{N} + (1-u_2(t))\hat{\beta}\frac{\hat{S}(I+k\hat{I})}{N} - (u_3(t)\psi + \gamma + \mu)I\bigg) \\
&+ \lambda_4(t)\bigg(u_3(t)\psi I - \hat{\gamma}\hat{I} - \mu\hat{I}\bigg) + \lambda_5(t)\bigg(\hat{\gamma}\hat{I} + \gamma I - \mu R\bigg).
\end{aligned}$$

Let $u_1^* = u_1^*(t)$, $u_2^* = u_2^*(t)$ and $u_3^* = u_3^*(t)$ be the control functions. When we apply the Pontryagin Maximum Principle [23], we obtain

$$\lambda_1' = -\frac{\partial H}{\partial S}, \quad \lambda_2' = -\frac{\partial H}{\partial \hat{S}}, \quad \lambda_3' = -\frac{\partial H}{\partial I}, \quad \lambda_4' = -\frac{\partial H}{\partial \hat{I}}, \quad \lambda_5' = -\frac{\partial H}{\partial R}, \tag{8}$$

with the final conditions $\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = 0$. To obtain an expression of the control functions, Hamiltonian is differentiated with respect to u as

$$\frac{\partial H}{\partial u_1}\bigg|_{u_1=u_1^*} = 0, \quad \frac{\partial H}{\partial u_2}\bigg|_{u_2=u_2^*} = 0, \quad \frac{\partial H}{\partial u_3}\bigg|_{u_3=u_3^*} = 0, \tag{9}$$

and we project the resulting equations onto the admissible set of control U. This optimality system is summarized as follows:

Theorem 3. Given an optimal control triple (u_1^*, u_2^*, u_3^*) and solution to the system (7) for (6), there exist adjoint variables $\lambda_i(t)$ for $1 \leq i \leq 5$ satisfying

$$
\begin{aligned}
\lambda_1'(t) &= \left((1-u_1(t))\beta(I+k\hat{I})\left(\frac{1}{N}-\frac{S}{N^2}\right)\right)(\lambda_1(t)-\lambda_3(t))+\lambda_1(t)\mu \\
&\quad+\left((1-u_2(t))\hat{\beta}\hat{S}\frac{(I+k\hat{I})}{N^2}\right)(\lambda_3(t)-\lambda_2(t))+u_3(t)(1-\epsilon)(\lambda_1(t)-\lambda_2(t)), \\
\lambda_2'(t) &= \left((1-u_1(t))\beta S\frac{(I+k\hat{I})}{N^2}\right)(\lambda_3(t)-\lambda_1(t)) \\
&\quad+(1-u_2(t))\hat{\beta}(I+k\hat{I})\left(\frac{1}{N}-\frac{\hat{S}}{N^2}\right)(\lambda_2(t)-\lambda_3(t))-\lambda_1(t)d+\lambda_2(t)(\mu+d), \\
\lambda_3'(t) &= -1+\left(\frac{1}{N}-\frac{(I+k\hat{I})}{N^2}\right)\Big((1-u_1(t))\beta S(\lambda_1(t)-\lambda_3(t)) \\
&\quad+(1-u_2(t))\hat{\beta}\hat{S}(\lambda_2(t)-\lambda_3(t))\Big)+\lambda_3(t)(u_3(t)\psi+\gamma+\mu) \\
&\quad-\lambda_4(t)u_3(t)\psi-\lambda_5(t)\gamma, \\
\lambda_4'(t) &= -1+\left(\frac{p}{N}-\frac{(I+k\hat{I})}{N^2}\right)\Big((1-u_1(t))\beta S(\lambda_1(t)-\lambda_3(t)) \\
&\quad+(1-u_2(t))\hat{\beta}\hat{S}(\lambda_2(t)-\lambda_3(t))\Big)+\lambda_4(t)(\hat{\gamma}+\mu)-\lambda_5(t)\hat{\gamma}, \\
\lambda_5'(t) &= \left(\frac{(I+k\hat{I})}{N^2}\right)\Big((1-u_1(t))\beta S(\lambda_3(t)-\lambda_1(t)) \\
&\quad+(1-u_2(t))\hat{\beta}\hat{S}(\lambda_3(t)-\lambda_2(t))\Big)+\lambda_5(t)\mu,
\end{aligned}
\tag{10}
$$

and $\lambda_i(T)=0$ for $i=1,2,\ldots,5$. Moreover, the optimal controls satisfy

$$
u_1^*(t)=\min\left\{\max\left\{0,\frac{-\beta S\frac{(I+k\hat{I})}{N}(\lambda_1-\lambda_3)}{w_1}\right\},0.95\right\},
$$

$$
u_2^*(t)=\min\left\{\max\left\{0,\frac{-\hat{\beta}\hat{S}\frac{(I+k\hat{I})}{N}(\lambda_2-\lambda_3)}{w_2}\right\},0.95\right\},
\tag{11}
$$

$$
u_3^*(t)=\min\left\{\max\left\{0,\frac{(1-\epsilon)S(\lambda_1(t)-\lambda_2(t))+\psi I(\lambda_3(t)-\lambda_4(t))}{w_3}\right\},1\right\}.
$$

FBS algorithm is used to solve the OCP numerically [23]. The algorithm firstly requires a control function taken from the set U in (5). The state equation firstly is solved forward in time. Then, the adjoint equation is solved backward in time. Afterwards, the optimality condition is recalculated at each iteration. This procedure is repeated iteratively, until the stopping criterion is satisfied. In the next section, we continue with some simulation results.

Simulation Results

Simulation results have been obtained by modifying the code of Silva et al. given in the study [25]. Indeed, the fourth-order Runge Kutta method is used for discretization of the model, while FBS method is incorporated to solve the OCP [23]. We fix the parameter values in the model and list them in Table 1.

Table 1. *Values of the parameters.*

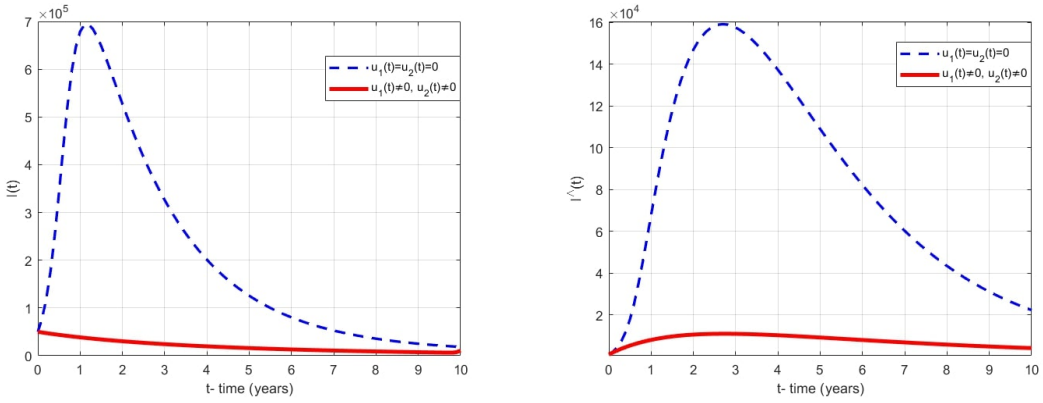
Parameters	Definition	Values
β	Transmission rate for S	5
$\hat{\beta}$	Transmission rate for $\hat{S}$	$(0.5) \times \beta$
γ	Recovery rate for I	0.29
$\hat{\gamma}$	Recovery rate for $\hat{I}$	0.5
μ	Mortality rate	$1/70$
d	Rate to return to $\hat{S}$	0.9
$\theta = r\psi$	Rate to enter $\hat{I}$	0.2188
$c = r(1-\epsilon)$	Rate to enter $\hat{S}$	0.0125
k	Self-protection rate of infected individuals	0.5
Σ	Recruitment rate	10000
M_1	Upper bound for u_1, u_2	0.95
M_2	Upper bound for u_2	1
r	Testing rate	0.25
ϵ	Test specificity	0.95
ψ	Test sensitivity	0.875

We compare three different intervention strategies. Firstly, we investigate the quarantine and isolation of the infected individuals by fixing the testing rate in the subsection of optimal control of quarantine and isolation strategies. Then, we proceed with the optimal testing rate, whereas quarantine or isolation are not put into action. Lastly, we consider the optimal quarantine and isolation together with the optimal testing strategy in the last subsection. The corresponding cost functionals are defined as J_1, J_2 and J_3, respectively.

Optimal control of quarantine and isolation strategies

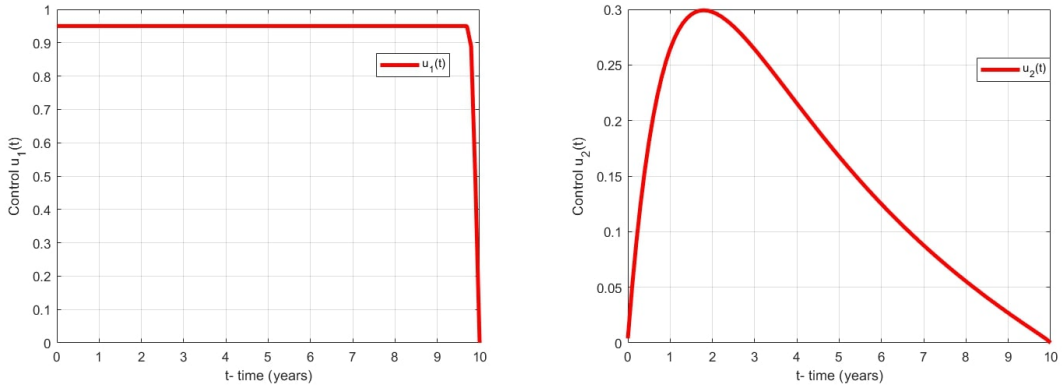
In the definition of the cost functional (6), w_1 and w_2 are positive weight constants associated with quarantine and isolation, respectively, where we fix $\omega_3 = 0$. We assume that the initial conditions $S(0) = 1000000$, $\hat{S}(0) = 100$, $I(0) = 50000$, $\hat{I}(0) = 1000$ and $R(0) = 10$.

We present the number of infected individuals with and without control in Fig. 1. The case before applying the optimal control strategy is shown as $u_1(t) = u_2(t) = 0$ with blue dashed lines, while solutions for which we apply the optimal control intervention are shown with red solid lines. We observe that the number of infected individuals $I(t)$ and $\hat{I}(t)$ decrease over time as a result of quarantine and isolation. As it can be seen in Fig. 2, quarantine or isolation must be applied for long time. In this case, it can be deduced that the epidemic is very severe and the number of death could be very high in case of no interventions. Therefore, quarantine or isolation must be implemented very seriously. Fig. 2 shows a strict application of quarantine, while it results in a more flexible isolation strategy. Susceptible but incorrectly identified individuals can protect themselves from infection, so this could be the main reason for such a relaxed intervention $u_2(t)$.



(*a*) I. (*b*) $\tilde{I}$.

Figure 1. *Case 1 - Model prediction with and without optimal intervention (Solid and dashed lines represent the cases with and without optimal control, respectively.).*



(*a*) $u_1(t)$. (*b*) $u_2(t)$.

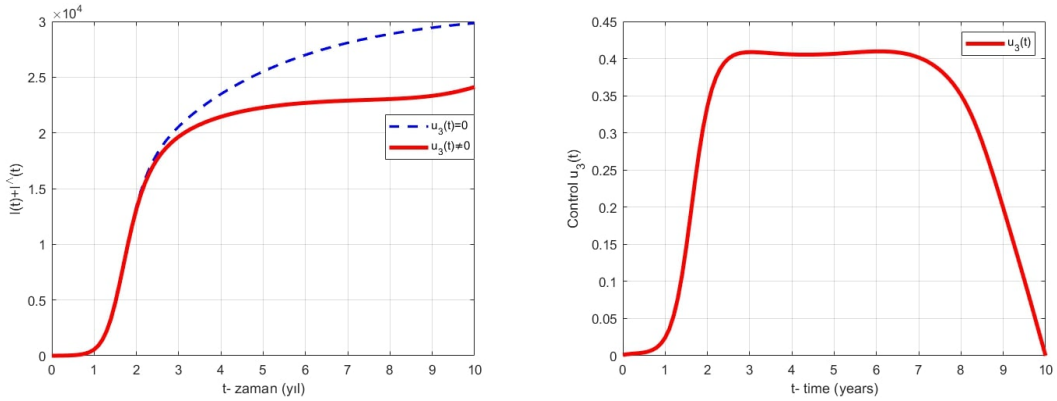
Figure 2. *Case 1 - Optimal control functions.*

Optimizing the testing rate

We proceed with the optimization of the testing rate, so we replace r with $u_3(t)$ in Eq. (7). The weights w_1 and w_2 are set as zero in the cost functional (6), while ω_3 is a positive constant. We choose the initial conditions as $S(0) = 1000$, $\hat{S}(0) = 0$, $I(0) = 1$, $\hat{I}(0) = 1$ and $R(0) = 0$. We assume that a limited number of tests are available, so $r = 0.0009$ is chosen for the uncontrolled case. We observe a decrease in the total number of infected individuals due to a higher testing rate in Fig. 3, while the testing rate reveals importance of testing in the peak of the epidemic. We conclude that after enough testing is conducted, testing speed can be reduced; but, the number of infected individuals is quite high, as it can be seen from Fig. 3. Therefore, quarantine or isolation strategies must be incorporated to slow down the spread.

Optimal control of quarantine and isolation strategies together with the testing rate

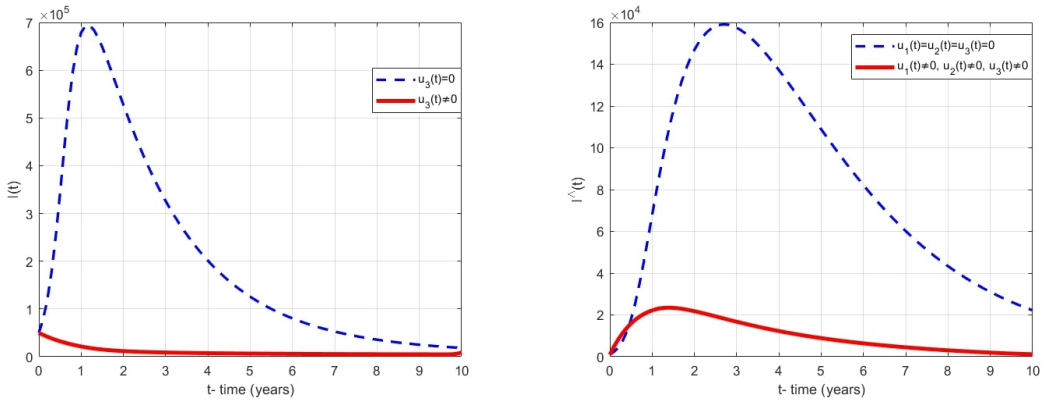
We aim to find an optimal control strategy to minimize the number of infected individuals by testing the individuals in the community together with quarantine and isolation. We set the values of three weight constants as positive values. We choose the initial conditions as $S(0) = 1000000$, $\hat{S}(0) = 100$,



(*a*) $I + \hat{I}$. (*b*) $u_3(t)$.

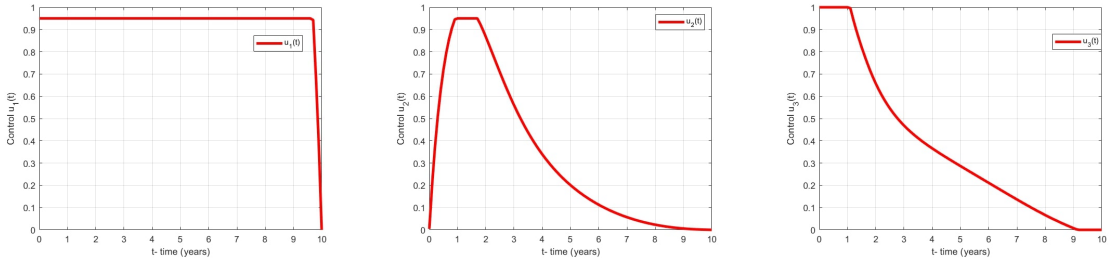
Figure 3. *Case 2 - Model prediction with and without optimal intervention (left) and the optimal control function (right) (Solid and dashed lines represent the cases with and without optimal control, respectively.).*

$I(0) = 50000$, $\hat{I}(0) = 1000$ and $R(0) = 10$.



(*a*) I. (*b*) $\tilde{I}$.

Figure 4. *Case 3 - Model prediction with and without optimal intervention (Solid and dashed lines represent the cases with and without optimal control, respectively.).*



(*a*) $u_1(t)$. (*b*) $u_2(t)$. (*c*) $u_3(t)$.

Figure 5. *Case 3 - The optimal control functions.*

In Fig. 4, the number of infected individuals (I and $\hat{I}$) decreases over time when three intervention strategies are implemented. It is observed that the impact of quarantine is very important (see Fig. 5), since it is applied on a long time interval. In addition, we see that it is vital to test people rapidly in the

beginning of the epidemic, and the test rate can be reduced over time.

In addition, we compare the values of the cost functionals J_1, J_2 and J_3 by fixing the initial conditions as $S(0) = 1000000, \hat{S}(0) = 100, I(0) = 50000, \hat{I}(0) = 1000, R(0) = 10$. We obtain that $J_1 = 3.2264e + 05$, $J_2 = 2.5333e + 06$ and $J_3 = 2.8691e + 05$, which gives us the order $J_3 < J_1 < J_2$. Optimizing quarantine/isolation and testing ensures the smallest value of J. The next best strategy is to apply quarantine/isolation via $u_1(t)$ and $u_2(t)$ (J_1). Therefore, applying three controls together gives better results than applying quarantine/isolation alone. When the testing rate is optimized only (J_2), the largest value of J is obtained. Therefore, we see that implementation of quarantine/isolation is inevitable.

Summary and conclusion

In this study, a mathematical model is constructed for an infectious disease, motivated by the work of Villela [21]. The DFE point of the model is derived and stability analysis is presented. Then, three OCPs are constructed to control the spread of disease. Indeed, the testing rate is optimized together with quarantine/isolation together or separately.We observe that applying three control strategies together gives better results than applying quarantine/isolation alone. If the testing rate is optimized and quarantine/isolation is not applied (J_2), the largest value of the cost functional is obtained.

Preventing contact between infected and susceptible individuals via quarantine/isolation is of great importance together with the optimal testing strategy. As a result of the simulations results, quarantine should be applied for a very long time in case of a severe epidemic. We acknowledge that quarantine for such long periods is not realistic; however, we believe that this study could motivate construction of new mathematical models with the use of real data by incorporating the idea of imperfect testing.

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Authors Contribution Authors contributed equally to the study.

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