

Research Article

Optimal Control of Multiple Transmission of Water-Borne Diseases

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A controlled SIWR model was considered which was an extension of the simple SIR model by adjoining a compartment (W) that tracks the pathogen concentration in the water. New infections arise both through exposure to contaminated water as well as by the classical SIR person-person transmission pathway. The controls represent an immune boosting and pathogen suppressing drugs. The objective function is based on a combination of minimizing the number of infected individuals and the cost of the drugs dose. The optimal control is obtained by solving the optimality system which was composed of four nonlinear ODEs with initial conditions and four nonlinear adjoint ODEs with transversality conditions. The results were analysed and interpreted numerically using MATLAB.

1. Introduction

Most of the major problems that humanity face in the twenty-first century are related to water quantity and/or quality issues. These problems are going to be more aggravated in future by climate change, resulting in higher water temperatures, melting of glaciers, and an intensification of the water cycle [1], with potentially more floods and droughts [2]. With respect to human health, the most direct and most severe impact is the lack of improved sanitation, and related to it is the lack of safe drinking water, which currently affects more than one-third of the global population. Additional threats include, for example, exposure to pathogens or to chemical toxicants via the food chain, for instance, the result of irrigating plants with contaminated water and of bioaccumulation of toxic chemicals by aquatic organisms, including seafood and fish or during recreation like swimming in polluted surface water.

Water-borne diseases are infectious diseases caused by pathogenic microorganisms that most commonly are transmitted in contaminated fresh water, whether in bathing, washing, drinking, or in the preparation of food. Though these diseases spread either directly or indirectly through flies or filth, water is the chief medium for spread of these diseases, and hence, they are termed as waterborne diseases. More than one-third of Earth's accessible renewable freshwater is consumptively used for agricultural, industrial, and domestic purposes [3]. As most of these activities lead to water contamination with diverse synthetic and geogenic natural chemicals, it comes as no surprise that chemical pollution of natural water has become a major public concern in almost all parts of the world.

The main acute disease risk associated with drinking water in developing and transition countries is due to pathogens, which include viruses, bacteria, and protozoa, which spread via the oral-fecal route [4]. These diseases are more prevalent in areas with poor sanitary conditions. *Campylobacter jejuni*, *Microsporidia*, *Yersinia enterocolitica*, *Cyclospora*, *Caliciviruses*, and environmental bacteria like *Mycobacterium* sp., *Aeromonas* sp., *Legionella pneumophila*, and multidrug-resistant *Pseudomonas aeruginosa* have been associated with waterborne illnesses. These pathogens travel through water sources and interfuse directly through persons handling food and water. The main distribution of many water-borne pathogens varies substantially from one country to another. Some pathogens such as *Vibrio cholerae*, Hepatitis E virus, and Schistosomiasis are restricted to certain tropical countries; others, such as Cryptosporidiosis and Campylobacteriosis, are probably widespread.

Rotavirus infections predominate in the winter months and account for approximately 140 million cases/year with 600,000–800,000 deaths/year [5]. Recent evidence on *Entamoeba histolytica* in children (Dhaka, Bangladesh), the causative agent of Amoebiasis (Amoebic dysentery), shows that infection occurred in 80 percentage of children over a four-year period with a reinfection rate of 53 percentage [6]. According to WHO records of infectious disease outbreaks in 132 countries from 1998 to 2001, outbreaks of waterborne diseases are at the top of the list, with cholera as the most frequent disease, followed by acute diarrhea and typhoid fever [7].

Recent literature related to this work has been discussed below. The literature on economic epidemiology is varied and growing, and there are several good surveys, such as Gersovitz and Hammer [8] and Klein et al. [9]. The earliest contribution, by Sanders [10], considered the treatment in different versions of the SIS model from a planner's perspective. Goldman and Lightwood [11] studied treatment in the controlled SIS model but considered different cost structures, that is, on the assumption that the medical authorities operate without an explicit budget constraint. Rowthorn [12] extended the analysis of the controlled SIS model, by considering how different kinds of budget constraints affect the optimal solution.

Arnone and Walling [13] presented the information on pathogen sources, health effects of waterborne pathogens, relevant water quality legislation, and an evaluation of pathogen indicators. Joh et al. [14] predicted that in the case of waterborne diseases, suppressing the pathogen density in aquatic reservoirs may be more effective than minimizing the number of infected individuals. Shannon et al. [15] have developed improved disinfection, decontamination, reuse, and desalination methods to work in concert to improve health, safeguard the environment, and reduce water scarcity, not just in the industrialized world, but in the developing world, where less chemical and energy intensive technologies are greatly needed. Batterman et al. [16] studied the historical practices and different disciplinary approaches to water-related infectious disease and proposed an interdisciplinary public-health-oriented systems approach to research and intervention design. Finally, they

illustrated using a case study that focuses on diseases associated with water and sanitation management practices in developing countries where the disease burden is the most severe. Schwarzenbach et al. [17] discussed the main groups of aquatic contaminants and their effects on human health and approached to mitigate pollution of freshwater resources. Rahman et al. [18] determined the antibiotic potential of the extracts of the leaf and stem of *Argemone mexicana* as a natural antimicrobial agent against the waterborne bacteria.

Joshi [19] described the interaction of HIV and T cells in the immune system, and he explored the optimal controls representing drug treatment strategies. Zhang et al. [20] studied the HIV virus spread model with control variables to maximize the number of healthy cells and to minimize the cost of chemotherapy. Castilho [21] studied the optimal strategies for a limited-cost educational campaign during the outbreak of an epidemic. Joshi et al. [22] have illustrated the idea of optimal control in two types of disease models by treating two examples. In the first example, they considered an epidemic model with two different incidence forms. In the second example, they illustrated a drug treatment strategy in an immunology model. Brocka and Xepapadeas [23] have illustrated the analytical methods for recursive infinite horizon inter-temporal optimization problems with three stylized applications. The first application is the optimal management of spatially connected human-dominated ecosystems. The second and third applications are harvesting of spatially interconnected renewable resources. Iacoviello and Liuzzi [24] studied the optimal control problem for SIR-epidemic model in which multiple controls, both for the susceptible and infected, are considered. Yan and Zou [25] discussed the application of the optimal and sub-optimal Internet worm control using Pontryagin's maximum principle. In this model, the control variable represents the rate of treatment to remove infectious hosts from circulation by filtering or disconnection from the Internet. Blayneh et al. [26] have studied the dynamics of a vector-transmitted disease using coupled deterministic models with two controls.

Rowthorn et al. [27] used a combination of optimal control methods and epidemiological theory for metapopulations to minimize the number of infected individuals during the course of an epidemic. They found an optimal path by an anti-MRAP strategy which satisfies Hamilton and transversality conditions. Bhattacharyya and Ghosh [28] studied the basic reproduction ratio, stability of the solutions under realistic biological parameters for the vertically transmitted diseases, and by the application of Pontryagin's maximum principle, they performed the optimal analysis of the control model considering the antiviral drug to the infective and vaccination to the susceptible as control parameters. Shirazian and Farahi [29] showed the implementation of mathematical models to formulate guidelines for clinical testing and monitoring of HIV/AIDS disease. Numerical results were obtained using mathematical softwares, LINGO and MATLAB. Prosper et al. [30] applied optimal control in the context of SAIR model with two controls, namely, social distancing and antiviral treatment, in minimizing the number of H1N1 infections in the seasonal and pandemic H1N1 influenza.

Rodrigues et al. [31] investigated the optimal vaccination strategy for the dengue epidemic considering both the costs of treatment of infected individuals and the costs of vaccination. The optimal control problem was solved using two methods: direct and indirect. The direct method uses the optimal functional and the state system and was solved by DOTcvpSB. It is a toolbox implemented in MATLAB, which uses numerical methods for solving continuous and mixed-integer dynamic optimization problems. The indirect method uses iterative method with a Runge-Kutta scheme and solved through ode45 of MATLAB. Tchuente et al. [32] derived the optimality system and used the Runge-Kutta fourth-order scheme to numerically simulate the treatment and vaccination efforts for the dynamics of

an influenza pandemic model. Zhang et al. [33] investigated an effective strategy to control the computer virus by setting an optimal control problem in the SIRA model. The optimality system is numerically solved by applying MATLAB with a Runge-Kutta fourth-order scheme.

To the best of our knowledge, optimal control theory has not been implemented to study waterborne diseases. The objective of the work is to find the optimal control of water borne diseases. The optimal control strategies in the form of immune boosting and pathogen suppressing drugs were used.

2. Optimal Control of Waterborne Disease Model

2.1. Mathematical Formulation

Consider the standard SIR model under the assumption of constant population size, together with a compartment W that measures pathogen concentration in a water source [34]. Susceptible individuals become infected either by contact with infected individuals or through contact with contaminated water. Infected individuals can in turn contaminate the water compartment by shedding the pathogen into W . An infected individual thus generates secondary infections in two ways: through direct contact with susceptible individuals and by shedding the pathogen into the water compartment, which susceptible individuals subsequently come into contact with it. The corresponding model equations are

$$\begin{aligned}\dot{S} &= \mu N - b_W WS - b_I SI - \mu S, \\ \dot{I} &= b_W WS + b_I SI - \gamma I - \mu I, \\ \dot{W} &= \alpha I - \xi W, \\ \dot{R} &= \gamma I - \mu R.\end{aligned}\tag{2.1}$$

Here, S represent the susceptible individual density, I represents the infected individual density, R represents the recovered/removed individual density, and W represents the pathogen concentration in water reservoir. Here, b_W and b_I are the transmission rate parameters for water-to-person and person-to-person contact, respectively. The birth and non-disease-related death rate is given by μ . The mean infectious period is given by $1/\gamma$. The pathogen shedding rate from infected individuals into the water compartment is given by α , and ξ gives the decay rate of pathogen in the water.

Rescaling the system of the model (2.1) gives dimensionless variables. Let N denote the total population size, and let $s = S/N$, $i = I/N$, $r = R/N$, $w = (\xi/\alpha N)W$, $\beta_W = b_W N \alpha / \xi$, and $\beta_I = b_I N$. The rescaled system is as follows:

$$\begin{aligned}\dot{s} &= \mu - \beta_w ws - \beta_i si - \mu s, \\ \dot{i} &= \beta_w ws + \beta_i si - \gamma i - \mu i, \\ \dot{w} &= \xi(i - w), \\ \dot{r} &= \gamma i - \mu r.\end{aligned}\tag{2.2}$$

Here, s represents the susceptible individual density in the total population for water-borne diseases, i represents the infected individuals with water-borne diseases among the total population, r represents the recovered or removed individual density from waterborne diseases among the total size of the population, w represents the pathogen concentration in the water reservoir, β_I represents the transmission parameters for the person-to-person contact rate, β_W represent the transmission parameter for the person-reservoir-person contact rate.

Consider the controlled $siwr$ model

$$\begin{aligned}\dot{s} &= \mu - \beta_w w s - \beta_i s i - \mu s + u_1 s, \\ \dot{i} &= \beta_w w s + \beta_i s i - \gamma i - \mu i, \\ \dot{w} &= \xi(i - w) + u_2 w, \\ \dot{r} &= \gamma i - \mu r,\end{aligned}\tag{2.3}$$

satisfying $s(0) = s_0$, $i(0) = i_0$, $w(0) = w_0$, and $r(0) = r_0$, where u_1 and u_2 are controls representing immune boosting and pathogen suppressing drugs, respectively.

The objective functional is defined as

$$J(u_1, u_2) = \int_0^T [i + A_1 u_1^2(t) + A_2 u_2^2(t)] dt,\tag{2.4}$$

where A_1 and A_2 are positive weights that balance the size of the terms. Here the number of infected individuals and cost of the immune boosting and pathogen suppressing drugs are minimized. The optimal control pair (u_1^*, u_2^*) were obtained such that

$$J(u_1^*, u_2^*) = \min_{(u_1, u_2) \in U} \left(\frac{J(u_1, u_2)}{(u_1, u_2)} \right),\tag{2.5}$$

where $U = \{(u_1, u_2) / u_i \text{ is measurable, } 0 \leq u_i \leq 1, t \in [0, T], \text{ for } i = 1, 2\}$ is the admissible control set.

2.2. Existence of an Optimal Control

The existence of the optimal control pair for the state system (2.3) can be obtained by using a result by Fleming and Rishel [35].

Theorem 2.1. *Consider the control problem with system (2.3). There exists $\bar{u}^* = (u_1^*, u_2^*) \in U$ such that*

$$\min_{(u_1, u_2) \in U} J(u_1, u_2) = J(u_1^*, u_2^*).\tag{2.6}$$

Proof. To use an existence result, Theorem III. 4.1 from [35], the following conditions should be satisfied:

- (1) the set of controls and corresponding state variables is nonempty;
- (2) the control set U is convex and closed;

- (3) the right-hand side of the state system is bounded by a linear function in the state and control variables;
- (4) the integrand of the objective functional is convex on U ;
- (5) The integrand of the objective functional is bounded below by $c_1(|u_1|^2 + |u_2|^2)^{\beta/2} - c_2$, where c_1, c_2 are positive constants and $\beta > 1$.

An existence result by Lukes [[36], Theorem 9.2.1 page 182] was used to give the existence of solutions of ODEs (2.3) with bounded coefficients, which gives condition 1. We note that our solutions are bounded. The control set is convex and closed by definition. Since the state system is bilinear in u_1, u_2 , the right-hand side of (2.3) satisfies-condition 3, using the boundedness of the solution. The integrand in the objective functional (2.4), $i + A_1 u_1^2(t) + A_2 u_2^2(t)$ is clearly convex on U . Moreover, there are $c_1, c_2 > 0$ and $\beta > 1$ satisfying

$$i + A_1 u_1^2(t) + A_2 u_2^2(t) \geq c_1 \left(|u_1|^2 + |u_2|^2 \right)^{\beta/2} - c_2 \quad (2.7)$$

because the state variables are bounded. We conclude that there exists an optimal control pair. \square

2.3. Characterization of the Optimal Control Pair

In order to derive the necessary conditions for the optimal control pair, the Pontryagin's maximum principle [37] was used.

The Hamiltonian is defined as follows:

$$H = \left(i + A_1 u_1^2 + A_2 u_2^2 \right) + p_1 (\mu - \beta_W w s - \beta_I s i - \mu s + u_1 s) + p_2 (\beta_W w s + \beta_I s i - \gamma i - \mu i) + p_3 [\xi(i - w) + u_2 w] + p_4 (\gamma i - \mu r). \quad (2.8)$$

Theorem 2.2. *Given optimal controls u_1^* and u_2^* and solutions s^*, i^*, w^* , and r^* of the corresponding state system (2.3), there exist adjoint variables p_1, p_2, p_3 , and p_4 satisfying*

$$\begin{aligned} \dot{p}_1 &= p_1 \beta_W w^* + p_1 \beta_I i^* + p_1 \mu - p_1 u_1^* - p_2 \beta_W w^* - p_2 \beta_I i^*, \\ \dot{p}_2 &= -1 + p_1 \beta_I s^* - p_2 \beta_I s^* + p_2 \gamma + p_2 \mu - p_3 \xi - p_4 \gamma, \\ \dot{p}_3 &= p_1 \beta_W s^* - p_2 \beta_W s^* + p_3 \xi - p_3 u_2^*, \\ \dot{p}_4 &= p_4 \mu, \end{aligned} \quad (2.9)$$

and $p_1(T) = p_2(T) = p_3(T) = p_4(T) = 0$, the transversality conditions. Furthermore,

$$\begin{aligned} u_1^* &= \min \left\{ \max \left\{ 0, -\left(\frac{p_1 s^*}{2A_1} \right) \right\}, 1 \right\}, \\ u_2^* &= \min \left\{ \max \left\{ 0, -\left(\frac{p_3 w^*}{2A_2} \right) \right\}, 1 \right\}. \end{aligned} \quad (2.10)$$

Proof. The form of the adjoint equations and transversality conditions are standard results from Pontryagin's maximum principle [37]. The adjoint system can be obtained as follows:

$$\begin{aligned}
 \dot{p}_1 &= - \left(\frac{\partial H}{\partial s} \right) = p_1 \beta_W w^* + p_1 \beta_I i^* + p_1 \mu - p_1 u_1^* - p_2 \beta_W w^* - p_2 \beta_I i^*, \\
 \dot{p}_2 &= - \left(\frac{\partial H}{\partial i} \right) = -1 + p_1 \beta_I s^* - p_2 \beta_I s^* + p_2 \gamma + p_2 \mu - p_3 \xi - p_4 \gamma, \\
 \dot{p}_3 &= - \left(\frac{\partial H}{\partial w} \right) = p_1 \beta_W s^* - p_2 \beta_W s^* + p_3 \xi - p_3 u_2^*, \\
 \dot{p}_4 &= - \left(\frac{\partial H}{\partial r} \right) = p_4 \mu.
 \end{aligned} \tag{2.11}$$

The optimality equations were given by:

$$\begin{aligned}
 \frac{\partial H}{\partial u_1} &= 2A_1 u_1^* + p_1 s^* = 0 \quad \text{at } u_1^*, \\
 \frac{\partial H}{\partial u_2} &= 2A_2 u_2^* + p_3 w^* = 0 \quad \text{at } u_2^*.
 \end{aligned} \tag{2.12}$$

Hence,

$$\begin{aligned}
 u_1^* &= - \left(\frac{p_1 s^*}{2A_1} \right), \\
 u_2^* &= - \left(\frac{p_3 w^*}{2A_2} \right).
 \end{aligned} \tag{2.13}$$

By using the bounds for the control u_1 , we get

$$u_1^* = \begin{cases} - \left(\frac{p_1 s^*}{2A_1} \right) & \text{if } 0 \leq - \left(\frac{p_1 s^*}{2A_1} \right) \leq 1, \\ 0 & \text{if } - \left(\frac{p_1 s^*}{2A_1} \right) \leq 0, \\ 1 & \text{if } - \left(\frac{p_1 s^*}{2A_1} \right) \geq 1. \end{cases} \tag{2.14}$$

In compact notation,

$$u_1^* = \min \left\{ \max \left\{ 0, - \left(\frac{p_1 s^*}{2A_1} \right) \right\}, 1 \right\}. \tag{2.15}$$

By using the bounds for the control u_2 , we get

$$u_2^* = \begin{cases} -\left(\frac{p_3 w^*}{2A_2}\right) & \text{if } 0 \leq -\left(\frac{p_3 w^*}{2A_2}\right) \leq 1, \\ 0 & \text{if } -\left(\frac{p_3 w^*}{2A_2}\right) \leq 0, \\ 1 & \text{if } -\left(\frac{p_3 w^*}{2A_2}\right) \geq 1. \end{cases} \quad (2.16)$$

In compact notation,

$$u_2^* = \min \left\{ \max \left\{ 0, -\left(\frac{p_3 w^*}{2A_2}\right) \right\}, 1 \right\}. \quad (2.17)$$

Using (2.15) and (2.17), we have the following optimality system:

$$\begin{aligned} \dot{s} &= \mu - \beta_w w s - \beta_i s i - \mu s + \min \left\{ \max \left\{ 0, -\left(\frac{p_1 s}{2A_1}\right) \right\}, 1 \right\} s, \\ \dot{i} &= \beta_w w s + \beta_i s i - \gamma i - \mu i, \\ \dot{w} &= \xi(i - w) + \min \left\{ \max \left\{ 0, -\left(\frac{p_3 w}{2A_2}\right) \right\}, 1 \right\} w, \\ \dot{r} &= \gamma i - \mu r, \\ \dot{p}_1 &= p_1 \beta_w w + p_1 \beta_i i + p_1 \mu - p_1 \min \left\{ \max \left\{ 0, -\left(\frac{p_1 s}{2A_1}\right) \right\}, 1 \right\} \\ &\quad - p_2 \beta_w w - p_2 \beta_i i, \\ \dot{p}_2 &= -1 + p_1 \beta_i s - p_2 \beta_i s + p_2 \gamma + p_2 \mu - p_3 \xi - p_4 \gamma, \\ \dot{p}_3 &= p_1 \beta_w s - p_2 \beta_w s + p_3 \xi - p_3 \min \left\{ \max \left\{ 0, -\left(\frac{p_3 w}{2A_2}\right) \right\}, 1 \right\}, \\ \dot{p}_4 &= p_4 \mu, \end{aligned} \quad (2.18)$$

$$s(0) = s_0, i(0) = i_0, w(0) = w_0, r(0) = r_0, \text{ and } p_1(T) = p_2(T) = p_3(T) = p_4(T) = 0. \quad \square$$

3. Numerical Results

In this section, the optimality system has been solved numerically, and the results have been presented. In this formulation, there were initial conditions for the state variables and terminal conditions for the adjoints. That is, the optimality system is a two-point boundary-value problem, with separated boundary conditions at times $t = 0$ and $t = T$. So the aim is to solve this problem for the value $T = 20$. This value was chosen to represent the time in hours at which treatment is stopped. An efficient method to solve two-point BVPs numerically is collocation. A convenient collocation code is the solver BVP4c implemented under MATLAB,

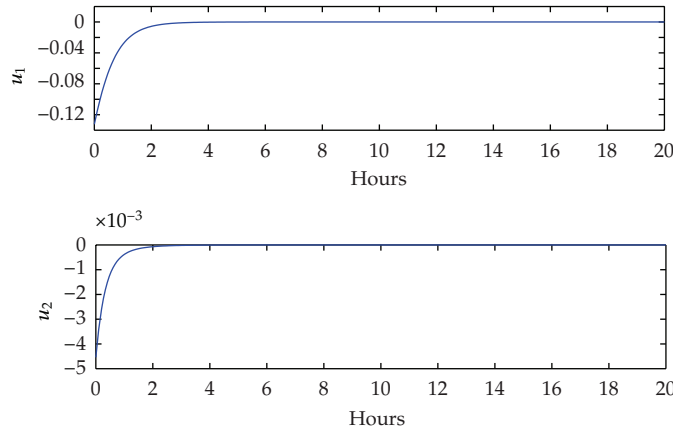


Figure 1: The optimal control graph for the two controls, namely, immune boosting and pathogen suppressing drugs.

which can be used to solve nonlinear two-point BVPs. It is a powerful method to solve the two-point BVP resulting from the optimality conditions.

The different variables in the objective functional (2.4), namely, the infected persons and the drug dosage, have different scales. Hence, they are balanced by choosing weighting values. Only if the value of A_1 is higher than the value of A_2 , the graphs are obtained correctly, whereas if the value of A_1 is lower than the value of A_2 , then the graphs are not obtained. Figures 1–3 are plotted using $A_1 = 25; A_2 = 10$.

The simulations were carried out using the following values taken from [34]: $\mu = 0; \beta_W = 0.6217; \beta_I = 0.6217; \gamma = 0.1340; \xi = 0.0333$. The initial conditions for the ordinary differential system were $s(0) = 1; i(0) = 1; w(0) = 1; r(0) = 0$. The transversality conditions for the ordinary differential system were $p_1(T) = 0; p_2(T) = 0; p_3(T) = 0; p_4(T) = 0$.

Figure 1 represents the controls u_1^* and u_2^* for the drug administration. The immune boosting drug is administered in full scale nearly up to 20 hours and then is tapered off. Similarly, the pathogen suppression drug is administered in full scale nearly up to 20 hours and then is tapered off.

The first figure represents the optimal path for the immune boosting control. The immediate rise of the curve from the negative part to the positive part is directly dependent upon the action of the immune response, which occurs shortly after treatment initiation in response to the high infection level. This implies that the optimal treatment actually happened. After that, the curve is constant in the positive level which denotes that the specific immune response is always maintained constant.

The second figure represents the optimal path for the pathogen suppressing drug. Here also the curve increases from the negative level to the constant positive level which denotes that the pathogen has suppressed fully and maintained that constant.

In Figure 2, the first figure represents the number of susceptible individuals during our treatment period. The susceptible individuals have a sharp decrease, and then after one or two hours, they become constant steadily. This clearly indicates that no other susceptible individuals become infected after the administration of the drugs.

The second figure represents the number of infected individuals during our treatment period. In the beginning, a sharp increase in the number of infected individuals has been

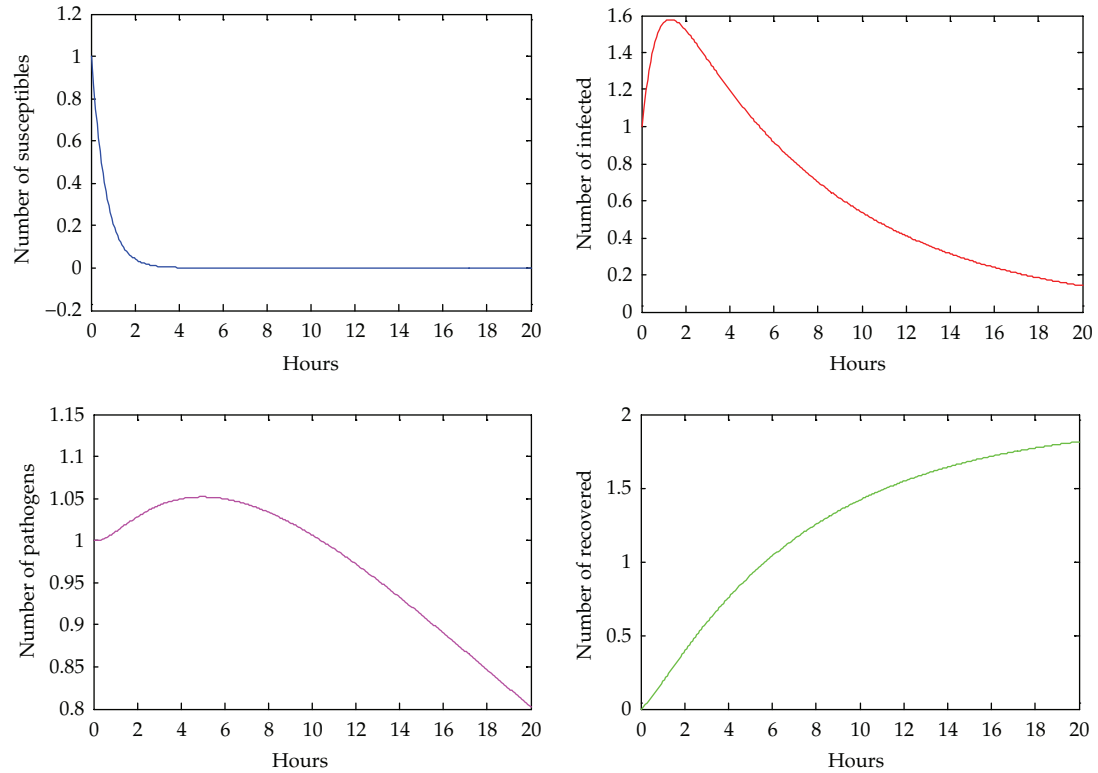


Figure 2: The effect of optimal control with the number of susceptibles, infected individuals, pathogen concentration, and the recovered individuals.

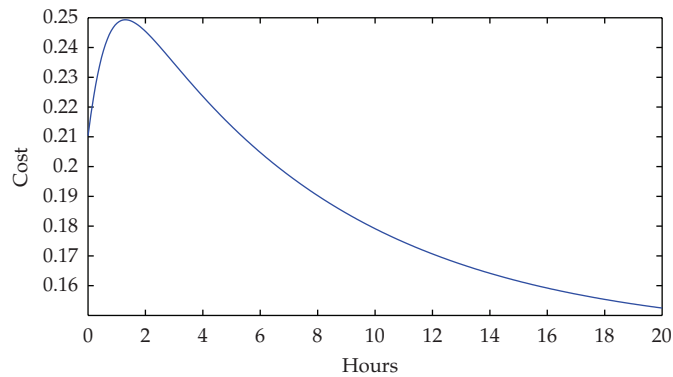


Figure 3: The optimal value of the cost of both the drugs.

observed because the drug takes some time to react with the infected individuals as they are highly infected by the pathogens, and then after one hour, it starts to decrease steadily linearly with time since the infected persons acquired immunity. It is possible to see that the controls, which means that everyone is vaccinated, imply that eradication of the disease.

The third figure represents the pathogen concentration during the treatment period. In the beginning, a steady increase in the curve has been observed which denotes an increase in

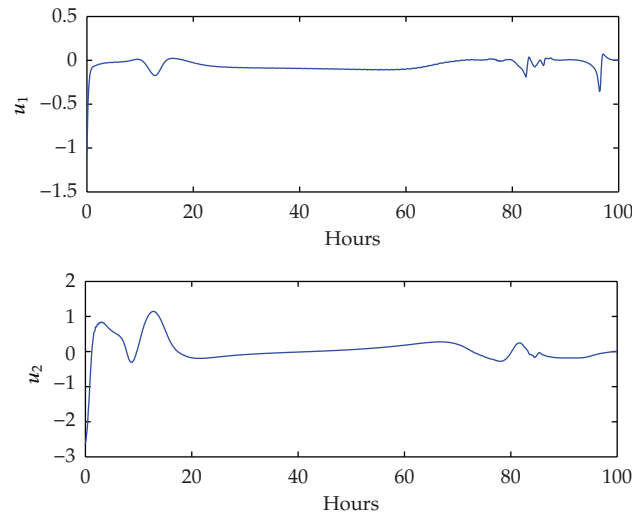


Figure 4: The optimal control graph for the two controls, namely, immune boosting and pathogen suppressing drugs.

the pathogen concentration as the pathogen adapts to the environment and grows efficiently in the absence of drugs. Then after few hours, it starts to decrease steadily since the pathogens have been suppressed by the drug.

The fourth figure represents the number of recovered individuals during our treatment period. A steady increase in the number of recovered individuals linearly with time has been noticed since the individuals have been recovered completely.

Figure 3 represents the cost of the optimal drug treatment. The curve increase to near their maximal level initially because in the high infection level, the dose of drugs will be large which in turn represents the cost of the drugs used. Then it drops off steadily which is because of the constant and steady eradication of the infection.

Figure 4 represents the controls u_1^* and u_2^* for the drug administration. The immune boosting and pathogen suppressing drugs are administered in full scale nearly up to 100 hours and then are tapered off.

The graph shows that the immune boosting and pathogen suppressing drugs are fully functional and active at 20 hours which is the critical point, and continuous administration of the drug beyond 20 hours proves pointless which could increase the cost of the drug, antibiotic resistivity, and other side effects which is shown in the graph as noise.

In Figure 5, the first figure represents the number of susceptible individuals during our treatment period. While the treatment is continued beyond 20 hours to 100 hours, the number of susceptible individuals increases which is due to the antibiotic resistance developed by the pathogen in the individuals.

The second figure represents the number of infected individuals during our treatment period. A sharp decrease and an increase in the number of infected individuals have been observed at the later stage of the therapy time due to the antibiotic resistance and the other pathological side effects caused by excess anti-pathogenic drugs.

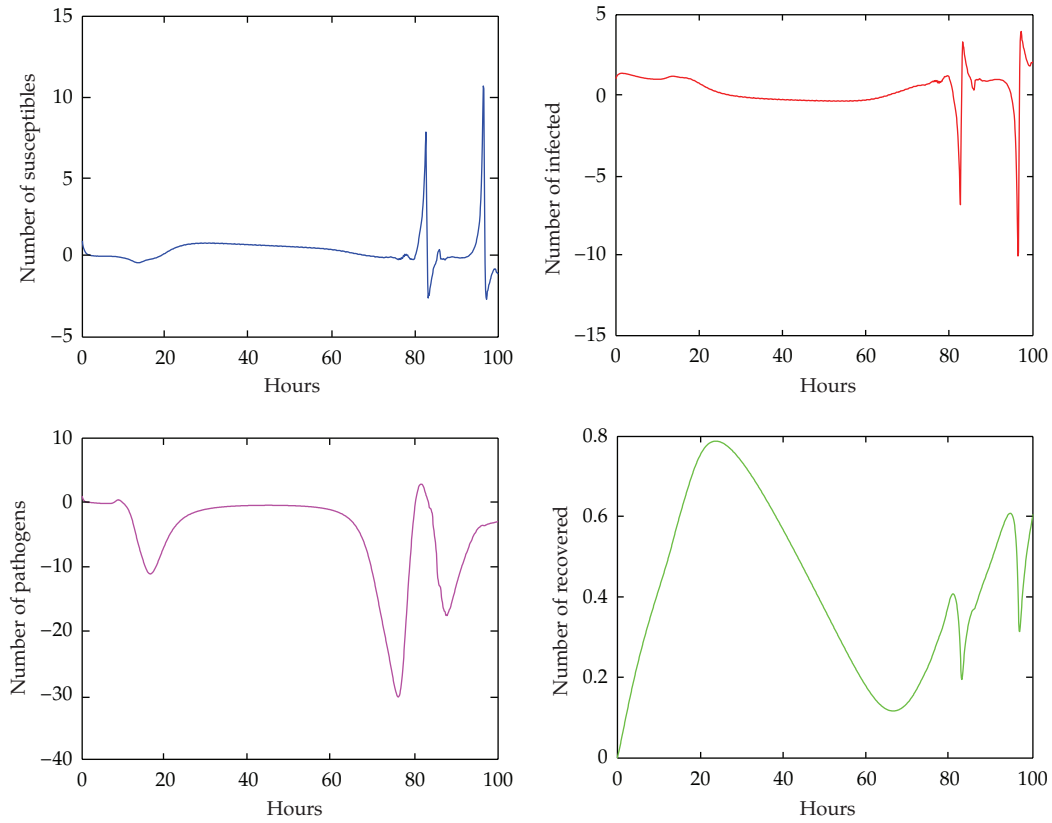


Figure 5: The effect of optimal control with the number of susceptibles, infected individuals, pathogen concentration, and the recovered individuals.

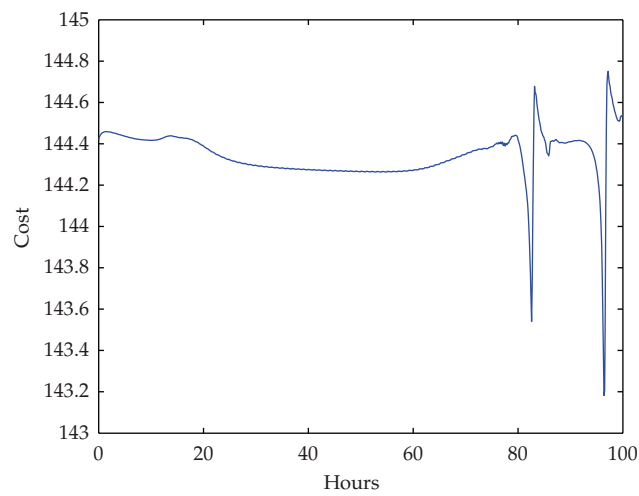


Figure 6: The optimal value of the cost of both the drugs.

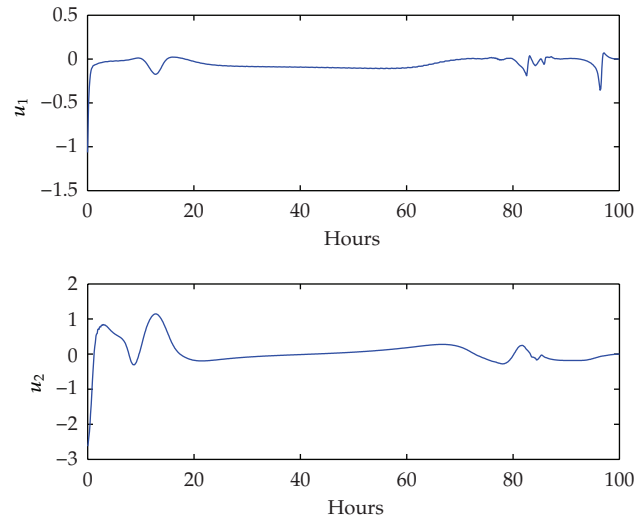


Figure 7: The optimal control graph for the two controls, namely, immune boosting and pathogen suppressing drugs.

The third figure represents the pathogen concentration during the treatment period. In the beginning, a steady increase in the curve has been observed which denotes an increase in the pathogen concentration as the pathogen adapts to the environment and grows efficiently in the absence of drugs. Then after few hours, it starts to decrease steadily since the pathogens have been suppressed by the drug. But after continuous administration of the drug, the pathogen gains resistivity against the drug and starts to grow luxuriously. Hence, the 20 hours is the critical period of the therapy, and continuing beyond 20 hours is not desirable.

Similarly, the fourth figure represents the number of recovered individuals during our treatment period. A steady increase in the number of recovered individuals linearly with time has been noticed since the individuals have been recovered completely. However if the treatment period is continued beyond 20 hours, the number of the recovered individuals gets reduced due to the side effects of the prolonged drug intake. Similar result, are observed for cost of the drug administration also (Figure 6).

The graphs were plotted for nonzero birth rate too. It was inferred from Figures 7, 8, and 9 that no changes were observed when compared to the zero birth rate graphs.

For non-zero birth rate ($\mu = 29$; the average birth rate in India per minute).

In the present study, it is shown that how both the vaccines resulted in minimizing the number of infected individuals and at the same time in a reduction of the budget related with the disease. One of the goals in this work is to develop a technique which could be used by the medical community to determine drug dosing tailored for individual patients. Determining such an optimal strategy would be of tremendous practical value, provided that reasonable estimates can be made for the parameter values for a given individual. To this end, a parameter-fitting exercise backed up by substantial experimental data would be very useful and could have a significant impact in improving drug therapy for a patient. It is hoped that the experiments will be performed to provide the data necessary for improved estimates on

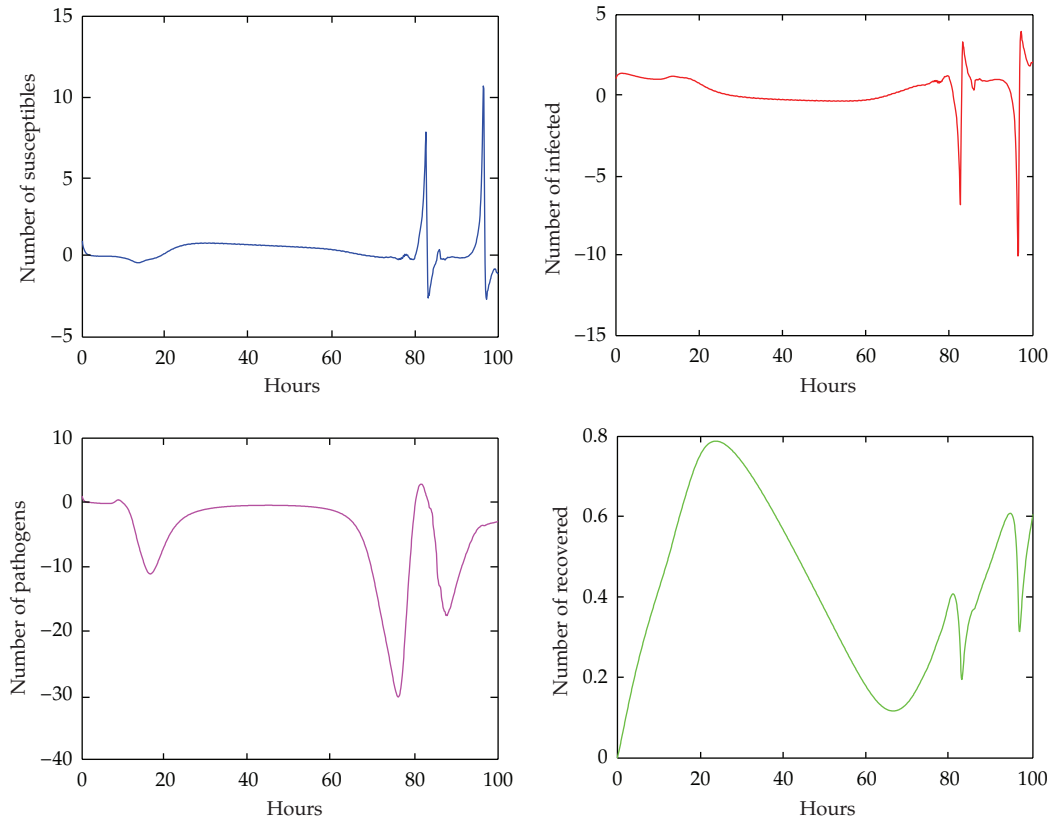


Figure 8: The effect of optimal control with the number of susceptibles, infected individuals, pathogen concentration, and the recovered individuals.

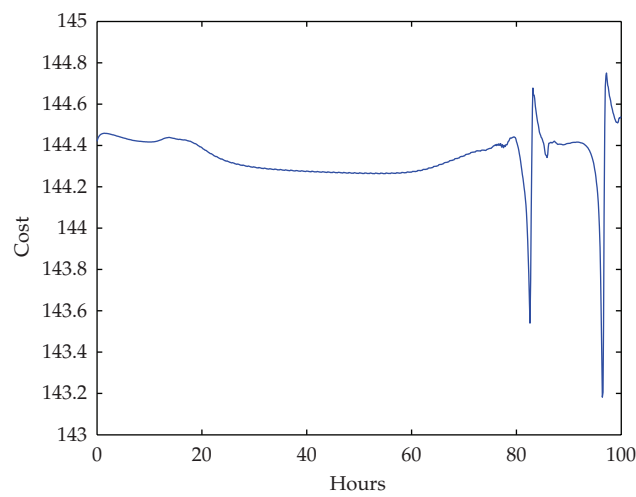


Figure 9: The optimal value of the cost of both the drugs.

some parameters, allowing for a more precise determination of optimal treatment protocols for patients.

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