An epidemic cholera model with control treatment and intervention

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Abstract. The mathematical modelling and dynamics optimization of cholera disease spread are discussed. The proposed SEIQR (Susceptible-Educated-Infected-Quarantined-Recovered) type model takes into account the bacterial concentration of the cholera spread dynamics. Three controls are considered to minimize the spread of cholera which are the treatment of quarantined populations and intervention efforts as a strategy in preventing the spread of disease through improved sanitation and education. Furthermore, the dynamics optimization problem is solved using the Pontryagin Minimum Principle method. The purpose is to decrease the populations of infected human populations and bacterial populations while minimizing the costs incurred for sanitation, educational and quarantine improvement. Numerical results are presented to show that the three controls can effectively minimize the spread of cholera.

1. Introduction

One of the most challenging issues for the survival of human populations other than war, starving and natural disasters is the spread of infectious diseases around the world. Infectious disease outbreaks cause millions of people to become ill and invest huge sums of money for health care systems([1],[2]). One of the infectious diseases carried by unhygienic water is cholera([2],[3],[4],[5],[6],[7]). Cholera is a diarrheal disease caused by intestinal infections with Vibrio cholerae bacteria with type O1 or O139 ([2],[6]). A susceptible person may be infected with choloreae bacteria if they consume unhygienic food or drink contaminated with vibrio choloreae([4],[5],[6],[8]). A person can be infected with mild symptoms or asymptoms([5],[6]). The main symptoms of cholera infection are many severe watery diarrhea, vomiting, leg cramps, decreased blood pressure, kidney failure, and if untreated leading to rapid dehydration, acidosis, circulatory collapse and death within 12-24 hours ([5],[6],[2],[9]). Some studies also say that people who recover only have immunity in a few weeks or months([5],[2]).

Cholera quickly spreads in densely populated areas, poor water sanitation and lack of clean water supply([9],[2],[10]). Therefore cholera disease is widely identified in poor and developing countries [6]. Cholera disease first appeared in India in 1817 [4]. Subsequently In 1961, cholera outbreaks began to enter Indonesia and for about 4 decades cholera epidemic began to emerge in the world [1]. V. cholerae bacteria infected 1.4 to 4.3 million people and 52 countries reported 142,311 cases of cholera and 4564 deaths in 2002([6],[1]). In 2007-2011 cholera outbreak occurred again in angola, haiti and zimbawe([3],[5]). Based on the above facts it appears that cholera is still a frightening infectious disease. Although cholera is a disease that appeared about 200
years ago and until now its control is still a challenge[8].

Mathematical modeling of the spread of cholera along with its control has been widely practiced in previous studies. ([1],[3], [5],[9]). In 2010 Neilan et al conducted an optimal intervention as a coping strategy for cholera disease. Interventions conducted on the research are vaccines, sanitation and rehydration medication. The aim of the research is to reduce the population of infected humans and reduce the bacteria with minimized cost expenditure by providing optimal control. In this study discussed human population in the form of susceptible, infected and recovered. In this model, the cholera-causing bacteria are divided into bacteria that have hyper infection and less infection so that in infected populations are also divided into mild and severe infections [8].

Furthermore, Mwasa et al conducted cholera modeling with public health intervention in 2011. Unlike Neilan, in this study vaccine and treatment not as control but rather made state population. In this study there are also state populations of people who have received learning about cholera so that the population is less likely to get the disease is also smaller. In this study there is also a population of quarantined persons where it is assumed that the learned person will be willing to be quarantined if it is suspected of having cholera.

Furthermore, Lemos-Paiao et al in 2016 discusses the spread of cholera disease model by providing control in the form of treatment (treatment) performed on population quarantined people. Treatment control is a treatment applied to infected populations with the aim of reducing the number of infected population cholera diseases. Infected populations subject to treatment will be quarantined so that there are quarantined populations.

In this paper will be reconstructed mathematical model of the spread of cholera disease by providing controls in the form of treatment, sanitation improvement and education about cholera. Giving control is done to reduce the number of population affected by cholera disease and reduce the proliferation of Vibrio Cholarae bacteria.

2. Mathematical Model

We propose models of type SEIQR (Susceptible-Education-Infectious-Quarantined-Recovered) and recognize the bacterial concentration for cholera spread. The dynamics equation splits the population of humans \( N(t) \) into six classes based on the disease condition, ie; susceptible population \( S(t) \), educated population \( E(t) \), asymptomatic population \( I_A(t) \), symptomatic population \( I_S(t) \), quarantined population \( Q(t) \) dan recovered population \( R(t) \). The bacterial aquatic (V. cholerae biomass level) population is \( B(t) \) which is the bacterial concentration at \( t \).

In this model the infected population does not consider the age and sex factors. It assumes that a positive recruitment rate of \( \Lambda \) on the susceptible population class \( S(t) \) and \( \mu \) natural mortality rate at \( t \) and applies to all human population. The susceptible population may be infected with cholera at the rate of transmission rate \( \beta \frac{B(t)}{k+B(t)} \). The consumption rate of bacteria through contaminated sources is \( \beta > 0 \), \( k \) is half the constant saturation for the population of bacterial, \( \beta \frac{B(t)}{k+B(t)} \) is a possibility that an infected individual has cholera disease due to contact with a contaminated source. Susceptible populations are educated at \( \psi \) and some educated populations can stop following preventive measures at \( \epsilon \), while very small numbers have cholera at \( \gamma \).

It is assumed that the infected population has an opportunity to have cholera disease with symptoms or asymptoms. Opportunities of \( p \) for infected populations with mild symptoms are classified as populations of asymptomatic infections (\( I_A \)). The infected population which has severe symptoms is classified as symptomatic infection (\( I_S \)).

Infected populations with mild symptoms are assumed to have less severe diarrhea so there is no death from cholera disease in this population. This population has a healing rate of \( \alpha_2 \). Unlike in the infected population with severe symptoms, it should accept themselves in the quarantine and subject to the right drug at \( \delta \). Quarantined individuals can recover with a heal-
ing rate of $\alpha_1$. The mortality rate caused by cholera diseases for infected individuals and in quarantine is $\mu_S$ dan $\mu_Q$. But those recovered can still lose immunity at a rate of $\nu$ and become susceptible again.

Every infected individual contributes to an increase in bacterial concentration at a rate of $\eta$. The concentration of bacterial may decrease at the death rate of $d$. It is common that when cholera-infected individuals release the Vibrio Cholorae bacteria back into the aquatic environment, it increases the spread of cholera [6].

In this model 3 controls are presented as a function of time with a reasonable upper and lower boundary conditions. First, $u_1(t)$ is a sanitation improvement to reduce the rate of bacterial uptake induced by an infected individual. Second, $u_2(t)$ is the proportion of population with severe symptomatic infection who receive treatment in quarantine until cured. Third, $u_3(t)$ is the increase of education to the susceptible population so that the number of infected population becomes reduced. Finally the mathematical model can be described as follows:

$$
\dot{S}(t) = \Lambda + \nu R(t) + \epsilon E(t) - \mu S(t) - u_3(t) \psi S(t) - (1 - u_1(t))\beta \frac{B(t)}{k + B(t)} S(t) \quad (1)
$$

$$
\dot{E}(t) = u_3(t) \psi S(t) - \epsilon E(t) - \mu E(t) - (1 - u_1(t))\gamma E(t) \quad (2)
$$

$$
\dot{I}_A(t) = (1 - u_1(t))\beta \frac{B(t)}{k + B(t)} S(t) + (1 - u_1(t))\gamma E(t) - \mu I_A(t) - \alpha_2 I_A(t) \quad (3)
$$

$$
\dot{I}_S(t) = (1 - u_1(t))(1 - p)\beta \frac{B(t)}{k + B(t)} S(t) + (1 - u_1(t))(1 - p)\gamma E(t) - \mu I_S(t) - \mu_S I_S(t) - u_2(t) \delta I_S(t) \quad (4)
$$

$$
\dot{Q}(t) = u_2(t) \delta I_S(t) - \mu Q(t) - \mu_Q Q(t) - \alpha_1 Q(t) \quad (5)
$$

$$
\dot{R}(t) = \alpha_1 Q(t) + \alpha_2 I_A(t) - \mu R(t) - \nu R(t) \quad (6)
$$

$$
\dot{B}(t) = \eta I_A(t) + \eta I_S(t) - dB(t) \quad (7)
$$

3. Optimal Control Problem

Generally the optimal control formulation considers a mathematical model or a dynamic system to be controlled which has a objective functional with boundary conditions and constraints ([11],[12],[13]). The set of state variables can be given as follows:

$$
\mathbf{x}(t) = (S(t), E(t), I_A(t), I_S(t), Q(t), R(t), B(t))^T.
$$

The spreading cholera dynamics is defined in equation (1)-(7) as plant for

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

with $\mathbf{x}(0) = \mathbf{x}_0$ as initial conditions.

In this case the controls were performed in the form of sanitation improvement, education and quarantine. The purpose of this problem is to seek optimal controls $\mathbf{u}^*(t) = (u_1(t), u_2(t), u_3(t))^T$ that aimed to minimize infected individuals, bacteria and the cost of removal from sanitation improvements, education and quarantine. The purpose of this problem can be formulated in the form of a cost function as follow

$$
J(\mathbf{x}, \mathbf{u}) = \int_0^T \left[ \frac{1}{2} C_1 I_{s1}^2(t) + \frac{1}{2} C_2 I_{s2}^2(t) + \frac{1}{2} C_3 B^2(t) + \frac{1}{2} C_4 u_1^2(t) + \frac{1}{2} C_5 u_2^2(t) + \frac{1}{2} C_6 u_3^2(t) \right] dt \quad (8)
$$

where $C_i > 0$ for $i = 1, 2, 3, 4, 5, 6$ is the price coefficient issued during the day period. The
first step in solving the optimal control problem using PMP is to determine the given hamiltonian function as follows: ([14],[15],[16])

\[
H = \frac{1}{2} C_1 I_1^2(t) + \frac{1}{2} C_2 I_2^2(t) + \frac{1}{2} C_3 B_3^2(t) + \frac{1}{2} C_4 u_1^2(t) + \frac{1}{2} C_5 u_2^2(t) + \frac{1}{2} C_6 u_3^2(t) \\
+ \lambda_1 (A + \nu R + \epsilon E - \mu S - u_3(t) \psi S(t)) - (1 - u_1(t)) \beta \frac{B(t)}{k + B(t)} S(t) \\
+ \lambda_2 (u_3(t) \psi S(t) - \epsilon E(t) - \mu E(t) - (1 - u_1(t)) \gamma E(t)) + \lambda_3 ((1 - u_1(t)) \beta \frac{B(t)}{k + B(t)} S(t) \\
+ (1 - u_1(t)) \rho \gamma E(t) - \mu I_A(t) - \alpha_2 I_A(t)) + \lambda_4 ((1 - u_1(t))(1 - p) \beta \frac{B(t)}{k + B(t)} S(t) \\
+ (1 - u_1(t))(1 - p) \gamma E(t) - \mu I_S(t) - \mu I_S(t) - u_2(t) \delta I_S(t)) + \lambda_5 (u_2(t) \delta I_S(t) - \mu Q(t) \\
- \mu Q(t) - \alpha_1 Q(t)) + \lambda_6 (\alpha_1 Q(t) + \alpha_2 I_A(t) - \mu R(t) - \nu R(t)) \\
+ \lambda_7 (\eta I_A(t) + \eta I_S(t) - dB(t)))
\]

(9)

where \( \lambda_i \) for \( i = 1, 2, 3, 4, 5, 6, 7 \) is a costate vector or lagrange multiplier that depends on the state. Next look for the optimal control value \( u_1^*, u_2^* \) and \( u_3^* \) as follows:

\[
u_1^*(t) = \frac{1}{C_1} (-\lambda_1 \beta \frac{B(t)}{k + B(t)} S(t) - \lambda_2 \gamma E(t) + \lambda_3 \beta \frac{B(t)}{k + B(t)} S(t) + \lambda_3 \rho \gamma E(t) \\
+ \lambda_4 (1 - p) \beta \frac{B(t)}{k + B(t)} S(t) + \lambda_4 (1 - p) \gamma E(t))
\]  

(10)

\[
u_2^* = \lambda_3 \delta I_S(t) - \lambda_3 \delta I_S(t) \\
C_2
\]

(11)

\[
u_3^* = \lambda_1 \psi S(t) - \lambda_2 \psi S(t) \\
C_3
\]

(12)

The optimal control \( u^* \) for sanitation, education and quarantine is obtained from \( \frac{\partial H}{\partial u} \) and has the following characteristics:

\[
u_1^* = max(u_{1min}, min(u_1^*, u_{1max})) \\
u_2^* = max(u_{2min}, min(u_2^*, u_{2max})) \\
u_3^* = max(u_{3min}, min(u_3^*, u_{3max}))
\]

Subsequently the equations (10). (11) and (12) are substituted into the equation (9) to have the optimal Hamiltonian function \( H^* \). Furthermore the Hamiltonian \( H^* \) is used to find the optimal state and costate equations ([14],[16]). The optimal state equations are given as follows:

\[
\dot{x}^* = \frac{\partial H^*}{\partial \lambda} \\
\dot{S}^* = \Lambda + \nu R + \epsilon E - \mu S - u_3^* \psi S(t) - (1 - u_1^*) \beta \frac{B(t)}{k + B(t)} S(t) \\
\dot{E}^* = u_3^* \psi S(t) - \epsilon E(t) - \mu E(t) - (1 - u_1^*) \gamma E(t) \\
\dot{I}_A^* = (1 - u_1^*) \beta \frac{B(t)}{k + B(t)} S(t) + (1 - u_1^*) \rho \gamma E(t) - \mu I_A - \alpha_2 I_A
\]

(13)

(14)
\[ I^*_S = (1 - u^*_1)(1 - p)\beta \frac{B}{k + B} S + (1 - u^*_1)(1 - p)\gamma E - \mu I_S - \mu_S I_S - u^*_2 \delta I_S \] (15)

\[ \dot{Q}^* = u^*_2 \delta I_S - \mu Q - \mu_Q Q - \alpha_1 Q \] (16)

\[ \dot{R}^* = \alpha_1 Q + \alpha_2 I_A - \mu R - \nu R \] (17)

\[ \dot{B}^* = \eta I_A + \eta I_S - dB. \] (18)

For the optimal costate equation is given as follows:

\[ \dot{\lambda} = -\frac{\partial H^*}{\partial x} \]

\[ \dot{\lambda}_1^* = -(\lambda_1 \mu - \lambda_1 u_3^* \psi - \lambda_1(1 - u_1^*) \beta \frac{B}{k + B} + \lambda_2 u_3^* \psi + \lambda_3(1 - u_1^*) \beta \frac{B}{k + B} + \lambda_4(1 - u_1^*)(1 - p)\beta \frac{B}{k + B}) \] (19)

\[ \dot{\lambda}_2^* = -(\lambda_1 \epsilon - \lambda_2 \mu - \lambda_2 \epsilon - \lambda_2(1 - u_1^*) \gamma + \lambda_3 p(1 - u_1^*) \gamma + \lambda_4(1 - u_1^*)(1 - p)\gamma) \] (20)

\[ \dot{\lambda}_3^* = -(C_1 I_A - \lambda_3 \mu - \lambda_3 \alpha_2 + \lambda_6 \alpha_2 + \lambda_7 \eta) \] (21)

\[ \dot{\lambda}_4^* = -(C_2 I_S - \lambda_4 \mu - \lambda_4 u_2^* \delta + \lambda_7 \eta) \] (22)

\[ \dot{\lambda}_5^* = -(\lambda_5 \mu - \lambda_5 \mu_q - \lambda_5 \alpha_1 + \lambda_6 \alpha_1) \] (23)

\[ \dot{\lambda}_6^* = -(\lambda_1 \nu - \lambda_6 \mu - \lambda_6 \nu) \] (24)

\[ \dot{\lambda}_7^* = -(C_3 B - \lambda_1(1 - u_1^*) \beta \delta k + \lambda_3(1 - u_1^*) \beta \delta k + \lambda_4(1 - u_1^*)(1 - p)\beta \delta k - \lambda_7 d) \] (25)

Finally the optimal state and costate have been obtained by solving the equation (13)-(25) taking into account \( x(0) = x_0 \) and \( \lambda(t_f) = 0 \).

4. Computational Results

The simulation results of the optimal control problem are given by solving the differential equation (13) - (25) using forward-backward sweep method to obtain optimal state and costate. The state system is completed using the forward order Runge-Kutta 4. Then the costate system is solved using backward runge kutta order-4. The state and costate values are used to update the control values using the characterization of each control and this process keeps repeating until the state, costate and control values have converged. Any parameter values used in this simulation are shown in Table 1. The optimal state is shown in Figure 1 and the optimal control is shown in Figure 2.

Figure 1 shows that asymptomatic and symptomatic infected population levels with controls decrease more rapidly than without control. Significant differences can be seen in about \( t = 20 \) days. In Figure 1 the asymptomatic infected population rate when \( t = 20 \) has increased to 800 soul. This increase is due to the large number of vulnerable populations without cholera-infected controls. Whereas under control, it appears that asymptomatic infected population rates continue to decline until the time-100 a day and when \( t = 20 \) is 504 inhabitants. Controls have an impact of 37% for asymptomatic infected populations. The rate of symptomatic infected population also increased by about \( t = 20 \) days with the sum of 669 soul. When controlled, it is seen that the symptomatic population level continues to decline until the time 100 a day and the symptomatic population when \( t = 20 \) days is 502 soul. Thus giving controls affects approximately 24% in symptomatic populations. The figure 1 also shows that the rate of bacterial concentration with the control also decreases faster than the concentration of uncontrolled bacteria. This is because when the level of asymptomatic and symptomatic infected populations decreases, it
Table 1. Parameter Value Model

| Parameter | Value       | Reference |
|-----------|-------------|-----------|
| \( \Lambda \) | 24.4N(0)/365000 | 5         |
| \( \mu \) | 2.2493 \times 10^{-3} | 5         |
| \( \beta \) | 0.08 | 5         |
| \( k \) | 10^6 | 5         |
| \( \nu \) | 0.4/365 | 5         |
| \( \delta \) | 0.05 | 5         |
| \( \epsilon \) | 0.003 | 6         |
| \( \psi \) | 0.008 | 6         |
| \( \gamma \) | 0.005 | 6         |
| \( p \) | 0.78 | 8         |
| \( \alpha_1 \) | 0.2 | 5         |
| \( \alpha_2 \) | 0.15 | 8         |
| \( \mu_S \) | 0.00127 | 8         |
| \( \mu_Q \) | 0.0001 | 5         |
| \( \eta \) | 50 | 8         |
| \( d \) | 1/30 | 8         |
| \( S(0) \) | 5750 | 5         |
| \( E(0) \) | 0 | assumed |
| \( I_A(0) \) | 1000 | assumed |
| \( I_S(0) \) | 700 | assumed |
| \( Q(0) \) | 0 | 5         |
| \( R(0) \) | 0 | 5         |
| \( B(0) \) | 275 \times 10^3 | 5         |
| \( u_1 \) | 0.001 - 0.4 | 8         |
| \( u_2 \) | 0 - 1 | assumed |
| \( u_3 \) | 0 - 1 | assumed |

causes a decrease in the supply of bacterial populations to multiply. The reduced bacterial population also causes the vulnerable population level to decrease.

The figure 2 explains that the optimal control \( u^* \) provides a fairly similar strategy in the 100 day range in cholera diseases. In Figure 2 it appears that a high level of sanitation is useful at the beginning of the outbreak to reduce the burst of infection. Figure 2 also explains that quarantine with maximum levels at the beginning of time is very effective in preventing death in symptomatic infection populations. The level of education is also given maximally to prevent vulnerable populations from becoming infected. Maximum scoring on all three controls for up to \( t = 100 \) days indicates that the magnitude of endemic cholera disease occurring in this case. But when the endemic diseases of cholera are not too large, then the value of control also continues to decline. These three controls cause infected populations and the population of bacteria to decrease significantly seen in Figure 1.

Figure 1 and Figure 2 indicate that the main objectives of optimal control problems in cases of cholera disease spread have been achieved, i.e. reducing the number of infected populations, bacterial populations and minimizing sanitation, education and quarantine costs. Thus the optimal provision of sanitation, education and quarantine causes the number of infected populations and bacterial populations to decline rapidly.
Figure 1. Population dynamics infected asymptomatic $I_A$, infected symptomatic $I_S$, bacterial $B$ and susceptible $S$.

Furthermore it is given how the spread of cholera disease after being controlled in the time of 100 a day can be seen in Figure 3. Based on the figure 3 it appears that the vulnerable population level has decreased since the beginning of time. This is due to the many vulnerable populations that interact with the contaminated environment of cholera bacteria to become infected populations. Significant declines in vulnerable population levels are also attributed to the control of education. In figure 3 it can be seen that the education population level has increased since the beginning of time and is inversely proportional to the vulnerable population level. In the educational population it is assumed to be exposed to cholera the possibility is very small because it has gained knowledge about cholera. Furthermore, the rate of infected population, especially symptomatic, continues to decline due to quarantine control. The amount of quarantine control from time to time $t = 100$ days leads to more populations of symptomatic infection put into quarantine than many vulnerable populations are infected. Quarantine is useful for treating symptomatic populations so that they recover quickly. In this case it appears that the population rate of recovered continues to increase since the beginning of time because of the large infected population experiencing healing. Asymptomatic and symptomatic infections continue to decrease as the rate of bacterial concentration increases only in not enough time. The level of bacterial concentration increases from the beginning of time to about $t = 40$ days. After that the rate of bacterial concentration continues to decline. Thus it appears that although control is focused on human populations, it indirectly affects the concentration of cholera bacteria.
5. Conclusion

Optimal control of sanitation, education and quarantine improvements in controlling the spread of cholera diseases has been discussed. Given differential equations as a dynamic system of cholera dispersion models that were divided into classes of human populations and bacterial populations.

In this paper optimal control problems are designed using the Pontryagin Minimum Principle which aims to minimize infected individuals, bacteria and reduce the cost of sanitation, education and quarantine. The simulation results are given at the end of the section to show the effect of
the given control. Based on the results, the number of infected individuals and bacteria have increased very large at certain times for the case without control. The controls reduced on the number of infected populations and bacterial population so that the cholera endemic disease could be minimized. This suggests that control strategies in the form of sanitation, education and quarantine improvements can have a good effect on minimizing the spread of cholera.

References
[1] Misra. A.K.,Gupta. A.,and Venturino. E.,Cholera dynamics with Bacteriophage infection: A mathematical study. *Chaos, Solitons and Fractals* (2016) 610-621.
[2] World Health Organization. Cholera Outbreak : Assessing the Outbreak Response and Improving Preparedness. (2004).
[3] Sun.G. dkk, Transmission Dynamics of Cholera: Mathematical Modelling and Control Strategies. *Communications in Nonlinear Science and Numerical Simulation* (2016)
[4] Dangbe.E., Irepran.D., Perasso.A., Bekolle.D., Mathematical modelling and numerical simulations of the influence of hygiene and seasons on the spread of cholera. *Mathematical Biosciences* (2017)
[5] Lemos-Paião. A.P., Silva. C.J., and Torres. D.F.M.,An epidemic model for cholera with optimal control treatment. *Journal of Computational and Applied Mathematics* (2016).
[6] Mwasa.A.,Tchuenche,.Mathematical analysis of a cholera model with public health interventions: *biosystems* 105 (2011) 190-200.
[7] Naşçy. A., dkk, Treatment and Vaccination Strategies to Control Cholera in Sub-Saharan Refugee Settings. *JAMA* (1998) Vol 279 N0.7
[8] Neilan Miller.L.Rachael,.Schaefer Elsa,.Graft.Holly,.Fister Renee.K.,Lenhart. S.,Modeling Optimal Intervention Strategies for Cholera.*Bulletin of Mathematical Biology* (2010) 72: 20042018.
[9] Cai.L., Modnak.C., Wang.J., An age-structured model for cholera control with vaccination. *Applied Mathematics and Computation* 299 (2017) 127140
[10] Sisodiya. S., Misra.O.P., Dhar.J., Dynamics of Cholera Epidemics with Impulsive Vaccination and Disinfection. *Mathematical Biosciences* (2018)
[11] Fitria.I., Winarni, Pancakahayani.A., Subchan, An Optimal Control Strategies using Vaccination and Fogging in Dengue Fever Transmission Model. *Mathematical Biosciences* (2017)
[12] Kirk.D.E., Optimal Control Theory: An Introduction. *New York: Englewood Cliffs, N.J (1970)*
[13] Sethi.S.P., Thompson.G.L, Optimal Control Theory: Application to Management Science and Economics. *USA (2000)*
[14] D.S. Naidu, Optimal Control System. *USA: CRC Press LLC (2002)*
[15] Lenhart.S., Workman.J.T., Optimal Control Applied to Biological Models. *London: CRC Press, Taylor and Francis Group (2007)*
[16] Subchan and R. Zbikowski,. Computational optimal control: Tools and practice. *John Wiley and Sons (2009)*