A mathematical model with isolation for the dynamics of Ebola virus

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A mathematical model with isolation for the dynamics of Ebola virus

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Abstract. In the absence of valid medicine and vaccine, isolation strategy is an important measure against Ebola virus outbreaks. In this paper, we present a deterministic compartmental model for assessing the impact of isolation to contain Ebola virus. The model includes the demographic effects, the latent undetectable and latent detectable compartments with isolation of infectious individuals. We study the outbreak of Ebola occurred in Sierra Leone. The numerical simulation shows that the isolation of latent detectable and infectious individuals is the most effective in curtailing the virus. Then, we present an optimal control problems subject to the model with the aim to derive the optimal isolation strategies. For each strategy, we study a specific objective in order to minimize not only the number of latent detectable and infected individuals but also the cost associated with the isolation program.

1. Introduction

Ebola virus is a highly contagious infectious disease, named after the Ebola River in the Democratic Republic of the Congo, where it was firstly discovered in 1976 [1, 2]. Previously, It was confined to Central Africa, but recently was also identified in West Africa mainly in Sierra Leone, Liberia and Guinea [1, 3].

The virus, previously known as Ebola hemorrhagic fever. Early symptoms of Ebola include: fever, headache, joint and muscle aches, sore throat, and weakness. Later symptoms include diarrhea, vomiting, stomach pain, hiccups, rashes, bleeding, and organ failure. When Ebola progresses to external and internal bleeding, it is almost always fatal [4, 5, 6, 7, 8]. Ebola virus is transmitted initially to human by contact with an infected animal's body fluid. It is most commonly spread by contact with blood and secretions, either via direct contact (through broken skin or mucous membranes in, for example, the eyes, nose, or mouth) with the infected individual or fluids on clothing or other surfaces, as well as needles [2, 9, 10, 11].

Mathematical modelling and optimal control theory have a powerful tool for investigating human infectious diseases, contributing to the understanding of the dynamics of diseases, providing useful predictions about the potential transmission of the virus and the effectiveness of possible control measures which can provide valuable information for public health policy makers.

The inclusion, in an epidemic model, of some practical control strategies, like vaccines, treatment or educational campaigns, provides a rational basis for policies designed to control the spread of the virus [12, 13, 14, 15, 16]. In this spirit, Rachah and Torres investigated an effective strategies to control the spread of Ebola virus by setting an optimal control problems in the case

of a SIR and SEIR models, where vaccine programs, treatment and educational campaigns, are the main practical strategies of their optimal control studies [17, 18, 19, 20].

Recently, many mathematical models have been used to investigate how to more effectively control emerging and re-emerging infectious disease control measures including vaccination and isolation [21, 22, 23, 24]. The mainly aim of public health policy is to decrease these burdens by reducing transmission or mitigating severity. For some infectious diseases, vaccines and antibodies have become primary tools as control measures. If a vaccines and antibodies are available for theses diseases, a vaccinated class that is protected at least partially ought to be included in the model development. But for an epidemic outbreak such as Ebola virus, where no vaccine protection is available, isolation is the main control measures available. In case of Ebola virus, the case of the French nurse cured of Ebola is a proof of the possibility of medical treatment but this medical treatment is not available for the poor countries who do not have the capacity to defend themselves against the virus, such as Sierra Leone, Liberia and Guinea. Then, the isolation is an important solution in curtailing the virus in these poor countries.

In this study, Isolation refers to the removal of latent detectable and infectious symptomatic individuals (yet exhibiting no clinical symptoms) from the general population. The use of isolation as primary control strategy presents significant logistical and economic strain on a public health system's resources.

The paper is organized as follows. In Section 2 we present the mathematical model to describe the dynamics of the Ebola virus by including the demographic effects, the latent undetectable and latent detectable compartments with isolation of infectious individuals. After the mathematical modelling, we present in Section 3 the numerical simulation of the model, in which we use vital dynamics parameters of Sierra Leone. Then, we use the obtained model to discuss it in Section 4 with several control strategies for the propagation of the virus. For each strategy, we study a specific objective in order to minimize not only the number of latent detectable and infected individuals but also the cost of the isolation program. We end with Section 5 of conclusions.

2. Mathematical model formulation

In this section, we present the mathematical model with isolation strategy as measure against Ebola virus. Let us firstly start by recalling the epidemiological model on which based our idea to add latent undetectable and detectable individuals, vital dynamics and isolation. It's the SEIR mathematical description of the transmission of Ebola virus, discussed by Rachah and Torres [18, 19]. It is based on the SEIR model, where the total population is subdivided into several compartments: Susceptible compartment $S(t)$ which denotes individuals who are susceptible to catch the virus and so might become infectious if exposed, Exposed compartment $E(t)$ which denotes the individuals who are infected but the symptoms of the virus are not yet visible, Infectious compartment $I(t)$ which denotes infectious individuals who are suffering the symptoms of Ebola and able to spread the virus through contact with susceptible classes of individuals, Recovered compartment $R(t)$ which denotes individuals who have immune to the infection, and consequently do not affect the transmission dynamics in any way when they contact other individuals [17, 20]. In the improvement of the SEIR model, we base our study on a deterministic ordinary differential equations (ODEs) epidemic model in which the total population N is divided into six mutually exclusive epidemiological classes: Susceptible individuals S, latent undetectable individuals E_1, latent detectable individuals E_2, infectious symptomatic individuals I, isolated individuals J, and individuals removed from isolation after recovery $R(t)$ which denotes the removed compartment, so that $N = S + E_1 + E_2 + I + J + R$.

In this model, susceptible individuals become infected and latent through contact with infectious individual at the rate $\dfrac{\beta\,(I + kJ)}{N}$, where β is the mean transmission rate per day, and k denotes the relative transmissibility of isolated individuals means it's a measure of the

effectiveness of isolation of infectious individuals. Latent undetectable individuals E_1 enter the latent detectable group E_2 at a rate σ_1, and become infectious symptomatic at a rate σ_2. We assume that the latent detectable group represent individuals with a viral load above the detection limit of the specific diagnostic test. Infectious individuals are isolated at the rate θ where Recovered individuals are removed from isolation after recovery at the rate γ. Furthermore, each group decreases at the natural death rate μ where the susceptible group increases at the natural birth rate. A schematic representation of the flow of individuals between the different classes is shown in the Figure 1.

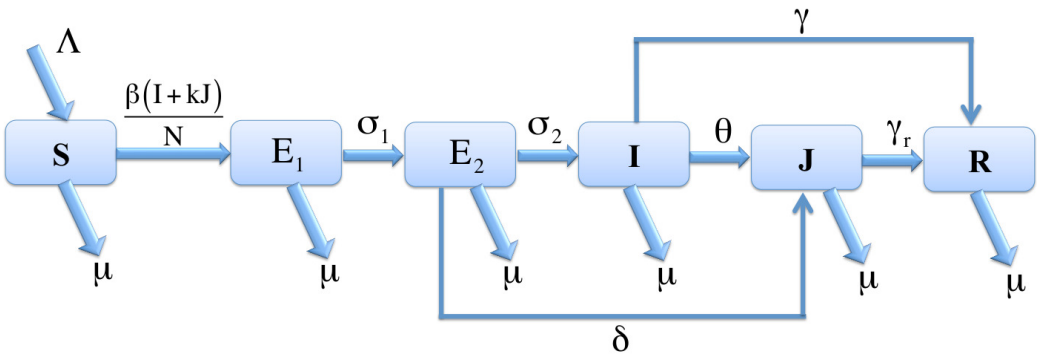


Figure 1: Shematic representation of the flow of individuals between the different classes.

The model is parametrized to the transmission dynamics of Ebola virus in West Africa by using published estimates. Let us start by describing the common parameters estimated in previous study of Ebola virus in West Africa. The mean incubation time $\frac{1}{\sigma_1}+\frac{1}{\sigma_2}$ is equal to 7 days where $\frac{1}{\sigma_1}=4$ days and $\frac{1}{\sigma_1}=3$ days [25, 26, 27]. The mean infection time is given by $\frac{1}{\theta}=5$ days [28, 29, 26]. The description of the rest of parameters is given in the Table 1. Now, let us specify that the trasmission rate is estimated in a study of Ebola virus occurred in Sierra Leone [30]. Furthermore, the estimation of the total population, the natural birth and death rates is available on the website *Statistiques Mondiales* [31]. The description of the transmission rate, the total population, the natural birth and death rates for Sierra Leone are given in the Table 2. The model is described by the following system of nonlinear ODEs:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda-\beta S(t)\left(\frac{I(t)+kJ(t)}{N}\right)-\mu S(t),\\
\frac{dE_1(t)}{dt} &= \beta S(t)\left(\frac{I(t)+kJ(t)}{N}\right)-(\sigma_1+\mu)\,E_1(t),\\
\frac{dE_2(t)}{dt} &= \sigma_1 E_1(t)-(\sigma_2+\delta+\mu)\,E_2(t),\\
\frac{dI(t)}{dt} &= \sigma_2 E_2(t)-(\theta+\gamma+\mu)\,I(t),\\
\frac{dJ(t)}{dt} &= \theta I(t)+\delta E_2(t)-(\gamma_r+\mu)\,J(t),\\
\frac{dR(t)}{dt} &= \gamma I(t)+\gamma_r J(t)-\mu R(t).
\end{aligned} \tag{1}$$

Table 1: Description of model parameters.

parameters	Description	values
k	Effectiveness of isolation of infectious	0.5
$\frac{1}{\sigma_1}$	Latent undetectable period	4 days
$\frac{1}{\sigma_2}$	Latent detectable period	3 days
$\frac{1}{\sigma_1}+\frac{1}{\sigma_2}$	Mean incubation time	7 days
$\frac{1}{\theta}$	Mean infection time	5 days
γ	Rate of recovery fom I to R	0.1
γ_r	Rate of recovery fom E_2 to R	0.2
δ	Rate of isolation fom E_2 to J	0.16

Table 2: Demographic effects and transmission rate in Sierra Leone [31].

parameters	Description	values for Sierra Leone
Λ	Birth rate	0.03703
μ	Death rate	0.01081
N	Total population	5879098
β	Transmission rate	0.344

Table 3: Description of initialization parameters in Sierra Leone [31].

Computational parameters	Desciption	Values for Sierra Leone
$S(0)$	$0.8 * N$	$4.7033.10^6$
$E_1(0)$	$0.05 * N$	$2.9395.10^5$
$E_2(0)$	$0.1 * N$	$5.8791.10^5$
$I(0)$	$0.05 * N$	$2.9395.10^5$
$J(0)$	0	0
$R(0)$	0	0

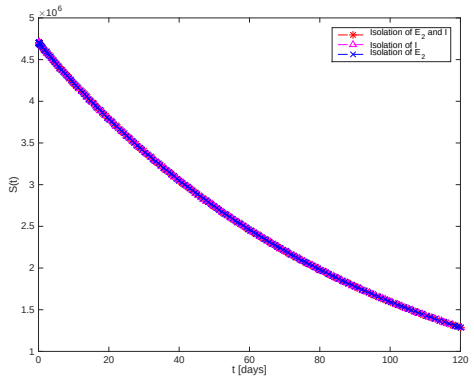
3. Numerical simulation

In this section, we study the impact of the isolation on Ebola virus outbreak occurred in Sierra Leone. In order to provide useful predictions about the potential transmission of the virus and the effectiveness of isolation, we study the numerical resolution of the model in several scenarios:

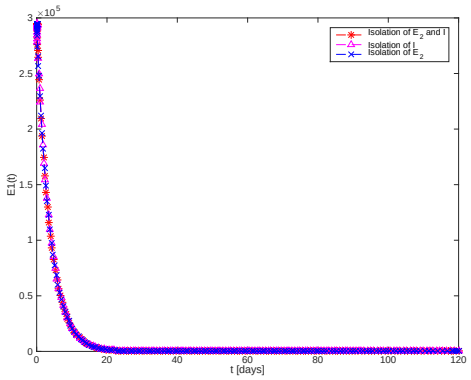
- Scenario 1: Isolation of latent detectable individuals only
- Scenario 2: Isolation of symptomatic infectious individuals only
- Scenario 3: Isolation of latent detectable and symptomatic infectious individuals

By comparing between the three scenarios, we can see the impact of isolation, in each scenario, on each class of individuals. The initializations are given by: $S(0) = 4.7033.10^6$, $E_1(0) = 2.9395.10^5$,

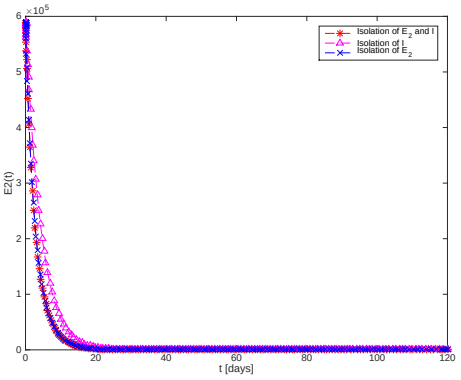
$E_2(0) = 5.8791.10^5$, $I(0) = 2.9395.10^5$, $J(0) = 0$ and $R(0) = 0$ [31]. Figure 2 shows, respectively,



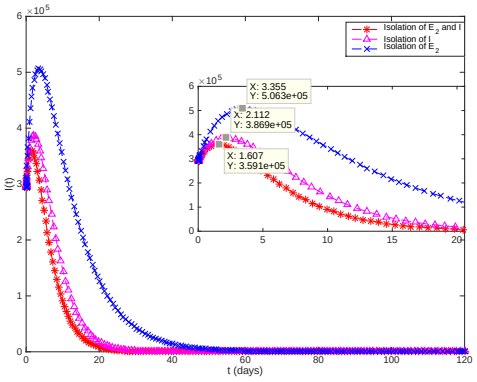
(a) Evolution of susceptible $S(t)$



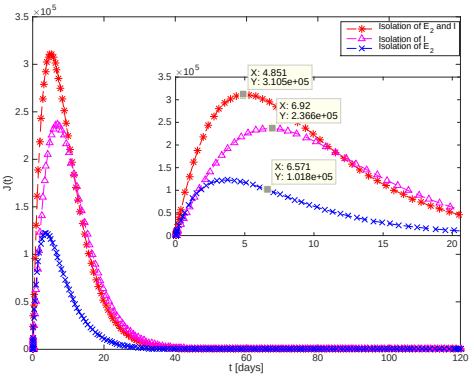
(b) Evolution of latent undetectable $E_1(t)$



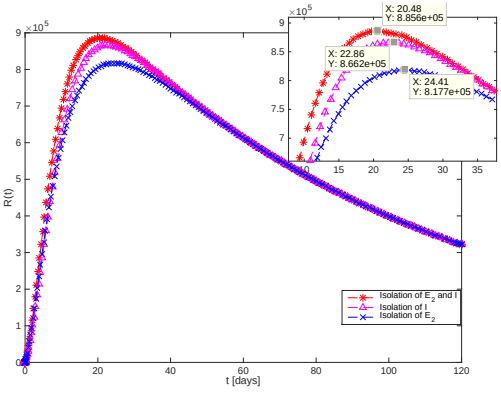
(c) Evolution of latent detectable $E_2(t)$



(d) Evolution of infectious $I(t)$



(e) Evolution of isolated $J(t)$



(f) Evolution of recovered $R(t)$

Figure 2: Evolution of individuals in compartments $S(t)$, $E_1(t)$, $E_2(t)$, $I(t)$, $J(t)$, $R(t)$ of the SE_1E_2IJR model (1) with vital dynamics for Sierra Leone.

the evolution of the susceptible, latent undetectale, latent detectable, infectious, isolated and recovered individuals, along time, in the three scenarios. By comparing between the three scenarios, in the Figure 2d, the time-dependent curve of infectious symptomatic individuals

shows that the peak of the curve of infectious symptomatic individuals is less important in case of isolation of latent detectable and infectious symptomatic individuals (scenario 3). In fact, the maximum value on the infectious symptomatic curve I in scenario 3 is $3.591.10^5$ individuals means 0.0611% of the total population, against $3.869.10^5$ means 0.0658% in case of isolation of symptomatic infectious only (scenario 2) and $5.063.10^5$ means 0.0861% in case of isolation of latent detectable only (scenario 3) (see Figure 2d). The percentage of symptomatic infectious 0.0611% of the scenario 3 correspond to the isolation of $1.018.10^5$ individuals (0.0173% of the total of population) (see Figure 2e). The percentage of symptomatic infectious 0.0658% of the scenario 2 correspond to the isolation of $2.366.10^5$ individuals (0.0402% of the total of population) (see Figure 2e). The percentage of symptomatic infectious 0.0861% of the scenario 1 correspond to the isolation of $3.105.10^4$ individuals (0.0528% of the total of population) (see Figure 2e). Then, as is shown in the Figure 2d and Figure 2e, the percentage of symptomatic infectious decreases by increasing the percentage of isolation. As shown in the Figure 2d), the impact is not only on the decreasing of number of infectious, but also in the period of infection which is the more shorter in the scenario 3. Figure 2f shows that the number of recovered individuals increases rapidly in case of scenario 3. In fact the maximum number of recovered in scenario 3 is $8.856.10^5$ aginst $8.662.10^5$ in scenario 2 and $8.856.10^5$ in scenario 1. In conclusion, one can say that Figure 2 shows the effectiveness of isolation of latent detectable and infectious symptomatic individuals in curtailing Ebola.

4. Optimal control problems

Recently, epidemiological models have used optimal control techniques, most of which focus on HIV disease and tuberculosis (TB) [13, 14, 24, 32, 33, 34]. The optimal control efforts are carried out to limit the spread of the disease, and in some cases, to prevent the emergence of drug resistance. In this section, we formulate two strategies of optimal control problems subject to the SE_1E_2IJR model (1), in order to derive the optimal isolation strategies. For each strategy, we study a specific objective in order to minimize not only the number of symptomatic infectious individuals or latent detectabe individuals but also the cost of the isolation program which includes the consumption for every individuals, the cost of organization, management and cooperation. The isolation of symptomatic infectious and latent detectabe individuals has a great importance in countries that don't have the capacity to defend themselves against the virus.

We compare the result of each strategy with the simulation results studied in section 3 for Sierre Leone. The so called Strategy 1, which is described in Section 4.1, consists on the control of the virus by minimizing the symptomatic infectious and isolated individuals with the isolation cost, which includes the cost of consumption for every individuals, the cost of organization, management and cooperation. Strategy 2 is an improvement of Strategy 1, is given in Section 4.2 and consists on the control of the virus by minimizing the symptomatic infectious, isolated and the latent detectable individuals with the isolation cost.

4.1. Strategy 1

In this section, we present a strategy of control of the virus by introducing into the model (1) a control $u(t)$ representing the isolation rate at time t. The control $u(t)$ is the fraction of symptomatic infectious individuals being isolated per unit of time. Then, the mathematical

model with control is given by the following system of nonlinear differential equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \beta S(t)\left(\frac{I(t)+kJ(t)}{N}\right) - \mu S(t),\\
\frac{dE_1(t)}{dt} &= \beta S(t)\left(\frac{I(t)+kJ(t)}{N}\right) - (\sigma_1+\mu)\,E_1(t),\\
\frac{dE_2(t)}{dt} &= \sigma_1 E_1(t) - (\sigma_2+\delta+\mu)\,E_2(t),\\
\frac{dI(t)}{dt} &= \sigma_2 E_2(t) - (u(t)+\gamma+\mu)\,I(t),\\
\frac{dJ(t)}{dt} &= u(t)I(t) + \delta E_2(t) - (\gamma_r+\mu)\,J(t),\\
\frac{dR(t)}{dt} &= \gamma I(t) + \gamma_r J(t) - \mu R(t).
\end{aligned} \tag{2}$$

The goal of the strategy is to reduce the symptomatic infectious individuals, the isolated individuals and the cost of isolation, which includes the cost of consumption for every individuals, the cost of organization, management and cooperation of the isolation program. Precisely, the optimal control problem consists of minimizing the objective functional

$$J(u) = \int_0^{t_{end}} \left[A_1 I(t) + A_2 J(t) + \frac{C_1}{2}u^2(t)\right] dt, \tag{3}$$

where $u(t)$ is the control variable, which represents the isolation rate at time t, t_{end} denotes the duration of the isolation program, A_1 and A_2 are positive balancing cost factors due to size and importance of the parts of the objective function. The total cost includes the consumption for every individuals, the cost of organization, management and cooperation. Hence, the cost function should be nonlinear. In this paper, a quadratic function is implemented for measuring the control cost by reference to many papers in epidemic control [35, 36, 37, 38, 39].

In the quadratic term of (3), C_1 is a positive weight parameter associated with the control $u(t)$, and the square of the control variable reflects the severity of the side effects of the vaccination. One has $u \in \mathcal{U}_{ad}$, where

$$\mathcal{U}_{ad} = \{u : u \text{ is measurable}, 0 \le u(t) \le u_{max} < \infty,\ t \in [0, t_{end}]\}$$

is the admissible control set, with $u_{max} = 0.9$.

4.2. Strategy 2

In this strategy, we study the effect of isolation of latent detectable. Our idea is based on taking into acount the severity of the virus. In fact, let us recall that Ebola virus spreads through human-to-human transmission, not only by close and direct physical contact with infected bodily fluids, but also via exposure to objects or contaminated environment. The most infectious fluids are blood, feces, and vomit secretions. However, all body fluids have the capacity to transmit the virus. Here, we intend to control the propagation of the Ebola virus by using two control variables into the SE_1E_2IJR model 1. Then, the mathematical model with control is given by

the following system of nonlinear differential equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \beta S(t)\left(\frac{I(t)+kJ(t)}{N}\right) - \mu S(t),\\
\frac{dE_1(t)}{dt} &= \beta S(t)\left(\frac{I(t)+kJ(t)}{N}\right) - (\sigma_1+\mu)\,E_1(t),\\
\frac{dE_2(t)}{dt} &= \sigma_1 E_1(t) - (\sigma_2+u_1(t)+\mu)\,E_2(t),\\
\frac{dI(t)}{dt} &= \sigma_2 E_2(t) - (u_2(t)+\gamma+\mu)\,I(t),\\
\frac{dJ(t)}{dt} &= u_2(t)I(t) + u_1(t)E_2(t) - (\gamma_r+\mu)\,J(t),\\
\frac{dR(t)}{dt} &= \gamma I(t) + \gamma_r J(t) - \mu R(t).
\end{aligned} \tag{4}$$

The goal of the strategy is to reduce the latent detectable individuals, the symptomatic infectious individuals, the isolated individuals and the cost of isolation, which includes the cost of consumption for every individuals, the cost of organization, management and cooperation of the isolation program. Precisely, the optimal control problem consists of minimizing the objective functional

$$J(u) = \int_0^{t_{end}} \left[B_1E_2(t) + B_2I(t) + B_3J(t) + \frac{C_2}{2}u_1^2(t) + \frac{C_3}{2}u_2^2(t)\right] dt, \tag{5}$$

subject to the system 1, where $u = (u_1, u_2)$, with u_1 representing the isolation control of latent detectable and u_2 the isolation control of symptomatic infectious individuals. The Lebesgue measurable control set is defined as

$$\mathcal{U}_{ad} := \{u = (u_1, u_2) : u \text{ is measurable, } 0 \le u_1(t),\, u_2(t) \le u_{max},\, t \in [0, t_{end}]\},$$

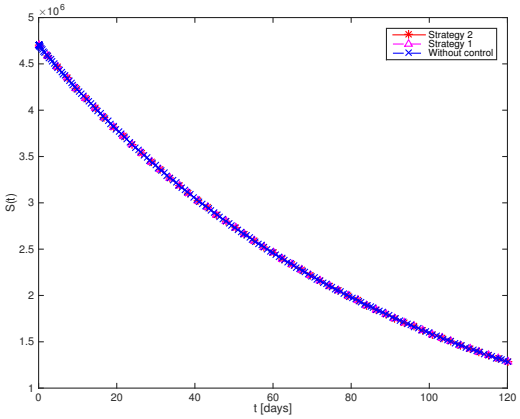
where $u_{max} = 0.9$, C_2 and C_3 are a positive weight parameters associated with the control $u_1(t)$ and $u_2(t)$. Here, we choose quadratic terms with respect to the controls in order to describe the nonlinear behavior of the cost of implementing the isolation program. The parameters B_1, B_2 and B_3 are positive balancing cost factors due to size and importance of the parts of the objective function. In the objective functional, the terms $B_1u_1^2/2$ and $B_2u_2^2/2$ represents the cost associated with the isolation program which includes the consumption for every individuals, the cost of organization, management and cooperation.

4.3. Discussion

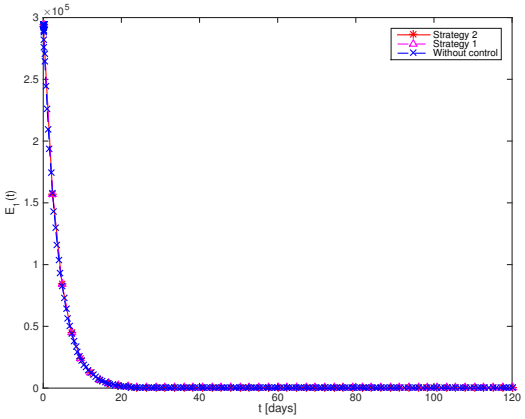
In this section we compare between the two strategies and the case without control, and we discuss the obtained results.

In order to compare the optimal control study of strategy 1 and strategy 2 with the numerical solution of the model 1 without control, we use here the same parameters, and the same initial values detailed in the tables 1, 2 and 3 for the initial number of susceptible, latent undetectable, latent detectable, symptomatic infectious, isolated and recovered populations. In the strategy 1, $t_{end} = 120\,days$, $C_1 = 200$, $A_1 = 1$ and $A_2 = 1$. In the strategy 2, the values of the parameters of the objective function are given by: $C_2 = 200$, $C_3 = 200$, $B_1 = 1$, $B_2 = 1$, $B_3 = 1$ where $t_{end} = 120\,days$.

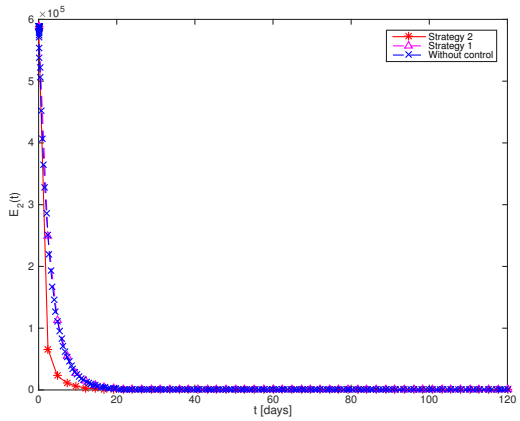
In our study of control of the virus, we use the parameters defined in the subsection 3. For the numerical solutions of the optimal control problems, we have used the ACADO solver [40], which is based on a multiple shooting method, including automatic differentiation and based ultimately



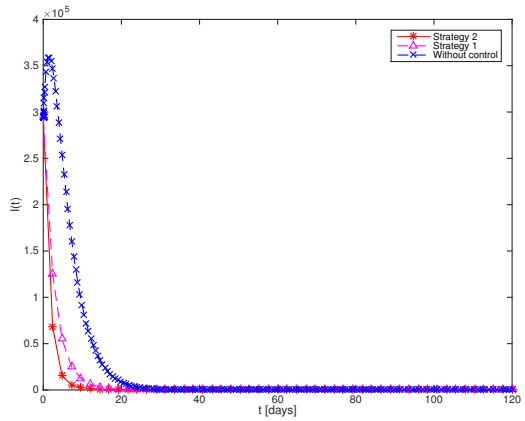
(a) Evolution of susceptible $S(t)$



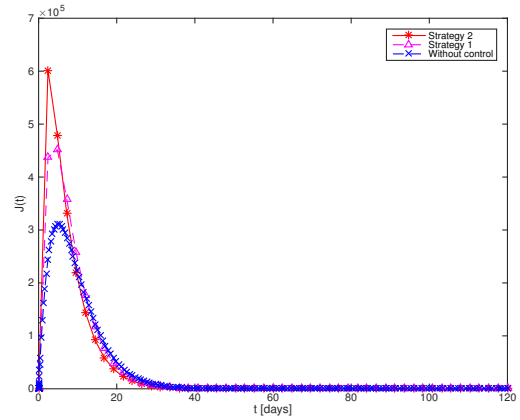
(b) Evolution of latent undetectable $E_1(t)$



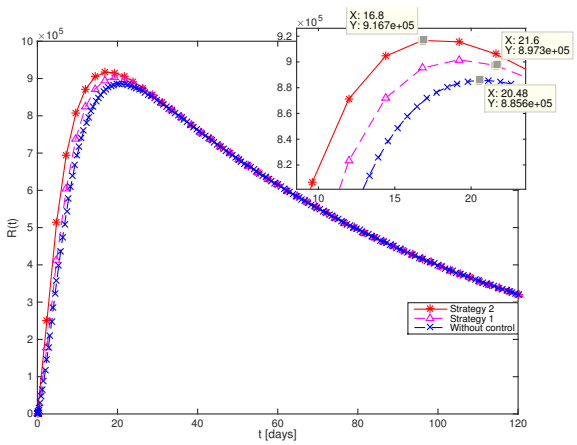
(c) Evolution of latent detectable $E_2(t)$



(d) Evolution of infectious $I(t)$



(e) Evolution of isolated $J(t)$



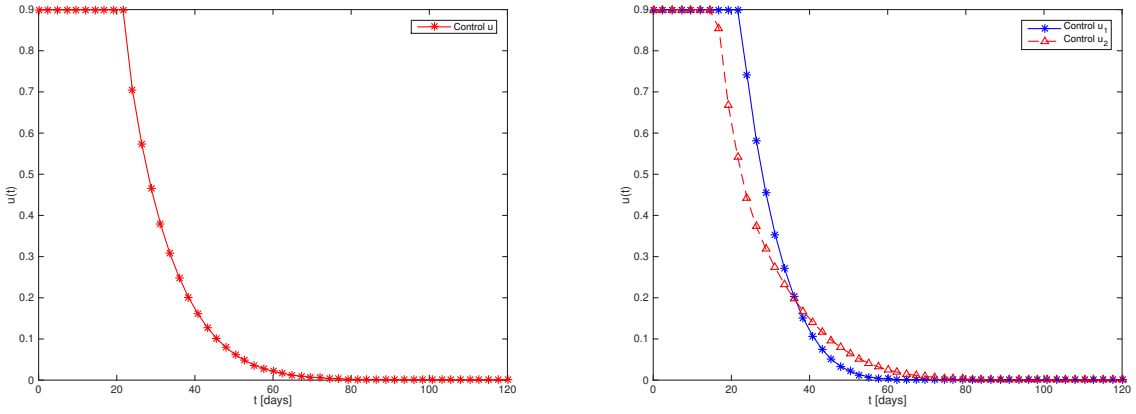
(f) Evolution of recovered $R(t)$

Figure 3: Comparison between the curves of individuals in compartments $S(t)$, $E_1(t)$, $E_2(t)$, $I(t)$, $J(t)$, $R(t)$ of the SE_1E_2IJR model (2) in case of control with Strategy 1, Strategy 2 and the case without control for the study of Sierre Leone.

on the semi direct multiple shooting algorithm of Bock and Pitt [41]. The ACADO solver comes as a self-contained public domain software environment, written in C++, for automatic control and dynamic optimization.

Figure 3 shows the time-dependent curves of susceptible, latent undectable, latent dtectable, symptomatic infectious, isolated and recovered individuals in case of control with Strategy 1 , control with Strategy 2 and the case without control, for the study of the population of Sierre Leone. In Figure 3c , we see that the number of latent dtectable E_2, in case of optimal control under Strategy 2, decreases more rapidly than the case of control with Strategy 1 and without control, during the isolation campaign. In Figure 3d, the time-dependent curve of symptomatic infectious individuals show that there is no peak of the curve of infectious individuals in case of control with Strategy 1 an Strategy 2, against the case without control in which an important peak exist. The same curves show that the period of infection is most shorter in case of control with Strategy 2. The period of infection, which is more shorter in case of strategy 2 than the strategy 1, is more shorter in case of strategy 1 than the case without control. This shows the efficiency of isolation control with Strategy 1 and Strategy 2 in controlling Ebola. Figure 3e presents the time-dependent curve of isolated individuals of Sierre Leone. By comparing the curve of symptomatic infectious I and the curve of isolated J, we see that the rapid decreasing of symptomatic infectious corresponds to the important increasing of isolated. Figure 3f shows that the number of recovered individuals increases more rapidly in case of control with strategy 2. The number of recovered increases more rapidly in case of control with strategy 1 than the case without control.

Figures 4a and 4b give respectively, a representation of the time dependent optimal control $u(t)$ for Strategy 1 and the time dependent optimal controls $u_1(t)$ and $u_2(t)$ in the isolation control study of Sierre Leone. In the two strategies, the controls variables stay at the upper bound during the beginning of the isolation program and start to decrease after.



(a) Strategy 1 (b) Strategy 2

Figure 4: The optimal control u for Strategy 1 and optimal control variables u_1 and u_2 for the study of Sierre Leone.

5. Conclusions

We investigated the SE_1E_2IJR model which describes the current detection of Ebola virus in Sierra Leone. The model includes the demographic effects, the latent undetectable and latent detectable compartments with isolation of infectious individuals. Our aim is to study the effect of

isolation in the absence of valid medicine and vaccine, against Ebola virus outbreaks. We studied the recent outbreaks of Ebola occurred in Sierra Leone by using it vital dynamics parameters. We resolved numerically the model and we showed that the isolation of latent detectable and infectious individuals is the most effective in curtailing the virus. Finally, we controled the propagation of the virus by reducing the not only the number of latent detectable and infected individuals but also the cost associated with the isolation program.

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