Modeling and control of an epidemic disease under possible complication

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***Abstract*—When dealing with epidemic spread, a very common and dangerous situation is the presence of an epidemic disease and a complication, especially in an elderly population or a weakened one. In this case the complication, that alone is not, in general, a fatal disease, may become risky. The ad hoc resource allocation becomes a mandatory task, aiming at the most rationale control strategy. This is the aim of this work, in which a new model is introduced; five classes are considered: the susceptible one, the class of people that has got the immunity from the first dangerous disease (but not from the complication), the class of patients with first disease, the class of those in the risky situation of having both the diseases, and the category of individuals with only the second disease that can still caught the first serious one. Control actions are introduced, as vaccination and medication, studying the effects of the different strategies. Preliminary simulation results evidenced the effectiveness of the proposed approach, allowing to determine a control strategy that reduces the number of dead, with an efficient resource allocation.**

***Index Terms*—interconnected epidemic diseases modeling, optimal control, vaccination**

I. Introduction

In this paper, the problem of controlling two interacting epidemics is faced aiming at an efficient resource allocation strategy. Epidemic modeling and control has been increasing its importance in the last few years for its capability in analyzing epidemic spread and suggesting the most effective strategy, [1]–[5]. The problem of controlling two epidemics spreads has been considered in different control frameworks, depending on the specificity of the diseases considered and, in particular, on the modalities of contagiousness. In [6] the concept of syndemic is discussed, enhancing the aspects of disease concentration, disease interaction and the social forces that give rise to them. The example of two epidemics not mutually causal is shown as well as the case in which the two epidemics have reciprocal relationships with each other and similar bidirectional relationship with the HIV epidemic. Two contemporary epidemic diseases have been considered in literature from different points of view, considering the case of distinct populations or the same population in which a second disease is overlying the first one and, besides less lethal, could become a serious complication. As examples of the first situation, an epidemiological analysis of migration is studied in [7], where in two distinct but interacting populations, local and migrants, a pathology spreads out and an optimal vaccination strategy is determined. A different framework is considered in [8] here one disease is spreading among two populations in interconnected regions. In the case in which infected individuals recover and can be reinfected, the best treatment action is to control preferentially the region with the lower level of infection and only when there is resource left over it is advisable to treat the other population. Sometimes the spread of some diseases is promoted by prior infection with another illness, as it happens with the HIV; this leads to complex patterns of epidemiological behaviour, as in [9]; the interesting result is that the best strategy to face the main disease is to reduce the infections upon which they depend. In [10] the interactions between two different diseases are discussed, the tuberculosis and the diabetes mellitus, showing that the diabetes mellitus is a risk factor for tuberculosis, and even that the latter may be caused by the diabetes. It is also evidenced how malnutrition, HIV, crowded living conditions and low level of hospitals contribute to high incidence of tuberculosis. A specific simulation study to analyze complications in case of a serious disease is proposed in [11], where the typhoid fever is modeled and many complications are considered, along with data about the population.

In this paper a different point of view is faced; it is considered a unique population with two pathologies: the serious one that may be transmitted only by contacts with infected patients; the other that may be fatal only when it becomes a complication of the first one. Moreover the latter yields an immunity, whereas the second one could be caught repeatedly. Therefore, five classes are considered: the subjects in the first category, that can caught both the pathologies; the subjects in the second class that have the immunity from the first contagious epidemic. Then there are three classes of patients: the first one with patients with only the dangerous contagious disease; the second one with both; then the the class of patients that has the second disease and could caught also the first one. Spontaneous healing is assumed as well as different birth and death rate from each classes. The two-

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epidemics model is controlled by using an optimal control strategy. The paper is organized as follows; in Section II the mathematical model proposed is discussed, whereas the optimal control problem formulation is introduced in Section III. Numerical simulations and discussions are proposed in Section IV, whereas conclusions are in Section V.

II. The mathematical model

The mathematical model proposed considers the possibility that, along with an infectious disease, a second pathology can be present, which is not particularly dangerous when it is the only one affecting the patients, but it can be particularly risky in combination with the infectious one. Typical examples are the HIV or the pneumonia that weaken a patient that consequently becomes vulnerable to other diseases (in general not so dangerous). This is also what happens to elderly population that are sensibly monitored and invited by the government to participate to vaccination's campaign, especially to avoid complications.

The starting point is a classical model for epidemic infectious like the SIR [12], in which the population is divided into *Susceptible* subjects, the ones that can be infected, *Infected*, the ill patients, and *Recovered*, the ones that are immune or by vaccination or after having been healed for the infection. The possibility to get the second pathology, for which non immunization is supposed, requires a deeper distinction between individuals and the introduction of two more classes. In fact, the infected patients can be divided according to two possible conditions, depending from the fact that they are or are not affected by the second pathology. Moreover, the possibility of being affected by the second pathology for susceptible subjects requires the introduction of a further class for the patients with the second pathology but not still immune from the epidemic disease. Then, five states are introduced:

- x_1: the individuals than can be infected by the contagious illness;
- x_2: the individuals immune from the contagious illness;
- x_3: the patients infected but not affected by the second pathology;
- x_4: the patients affected by both the pathologies;
- x_5: the patients affected by the second pathology only, non immune from the infectious illness.

Individuals x_1 and x_2 can become affected by the second pathology. The epidemic diffusion depends on the contacts and the interactions between infected (x_3 and /or x_4) and non immune individuals (x_1 and / or x_5). The contagious rate is denoted by β and depends on the number of possible dangerous contacts and on the probability of virus transmission; without particular assumptions, it is assumed the same for any interaction term. The second pathology (the complication) can occurr with a rate α_{ij}, where the pedices denote the transition from the state i to the state j; these rates can be assumed different, to put in evidence the differences between healthy people and infected ones. It is assumed that the recovery from the second illness can be also spontaneous from the x_5 class, and the rate of autonomous healing is denoted again with he coefficients α_{51}, being a natural transition proportional to the number of subjects.

Four control actions are considered:

i. u_1 represents the action devoted to vaccinate healthy non immune individuals x_1, making them transit to the x_2;
ii. u_2 is the therapy action over the patients in x_3;
iii. u_3 is the therapy action over the patients in x_4;
iv. u_4 the therapy for the second illness, applied to x_5.

Each control u_i is proportional, by a coefficient γ_i, to the number of subjects on which it directly acts. In each compartment new incomers μ_i and a percentage of removed people, $\delta_i x_i$, are included. Then, the resulting mathematical model describing the evolution of an epidemic with possible degeneration by a second pathology is

$$\begin{aligned}
\dot{x}_1 &= -\beta x_1 x_3 - \beta x_1 x_4 - \alpha_{15} x_1 + \alpha_{51} x_5 \\
&\quad -\gamma_1 x_1 u_1 + \gamma_4 x_5 u_4 - \delta_1 x_1 + \mu_1 \\
\dot{x}_2 &= \gamma_1 x_1 u_1 + \gamma_2 x_3 u_2 + \gamma_3 x_4 u_3 - \delta_2 x_2 + \mu_2 \\
\dot{x}_3 &= \beta x_1 x_3 + \beta x_1 x_4 - \alpha_{34} x_3 - \gamma_2 x_3 u_2 \\
&\quad -\delta_3 x_3 + \mu_3 \\
\dot{x}_4 &= \alpha_{34} x_3 + \beta x_4 x_5 + \beta x_3 x_5 \\
&\quad -\gamma_3 x_4 u_3 - \delta_4 x_4 + \mu_4 \\
\dot{x}_5 &= \alpha_{15} x_1 - \alpha_{51} x_5 - \beta x_4 x_5 - \beta x_3 x_5 \\
&\quad -\gamma_4 x_5 u_4 - \delta_5 x_5 + \mu_5
\end{aligned} \tag{1}$$

which is shown in Figure 1.

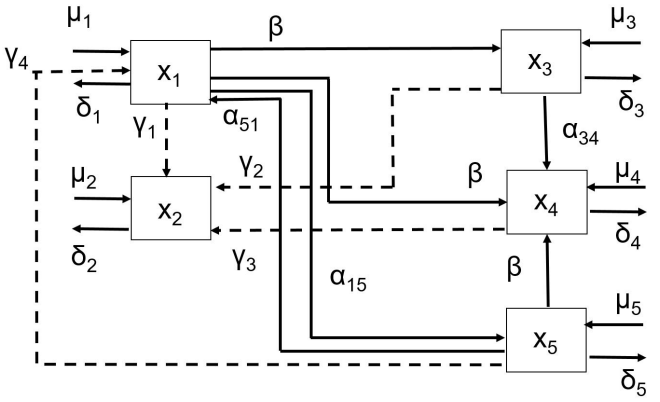

Fig. 1. Block diagram of the considered model.

III. Formulation of the optimal control problem

An optimal control problem is defined for the containment of the epidemic spread, with particular attention to the patients with the two pathologies; this approach suggests the best strategy to allocate properly the resources, also distinguishing between the different level of illness. The necessity of containing the number of infected individuals and the cost of the intervention suggest the introduction of a cost index which weights both the number of infected individuals and the control cost. Denoting the state x by $x = \begin{pmatrix} x_1 & x_2 & x_3 & x_4 & x_5 \end{pmatrix}^T \in R^5$

and the control $u = \begin{pmatrix} u_1 & u_2 & u_3 & u_4 \end{pmatrix}^T \in R^4$, a classical quadratic structure is chosen and the cost function adopted is

$$J = \frac{1}{2} \int_{t_0}^{t_f} \left(x^T Q x + u^T R u \right) dt \tag{2}$$

with

$$Q = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & q_3 & 0 & 0 \\ 0 & 0 & 0 & q_4 & 0 \\ 0 & 0 & 0 & 0 & q_5 \end{pmatrix} R = \begin{pmatrix} r_1 & 0 & 0 & 0 \\ 0 & r_2 & 0 & 0 \\ 0 & 0 & r_3 & 0 \\ 0 & 0 & 0 & r_4 \end{pmatrix} \tag{3}$$

denoting with q_i, $i = 3, 4, 5$ and with r_i, $i = 1, .., 4$ the weights of the state variables and the control respectively. No constrain has been introduced on the control amplitude, whose maximum value is defined through the minimization procedure on (2), the final time t_f is fixed while the final state value is left free. From (1) and (2), the corresponding Hamiltonian is

$$\begin{aligned} H &= \frac{1}{2} \left(q_3 x_3^2 + q_4 x_4^2 + q_5 x_5^2 + r_1 u_1^2 + r_2 u_2^2 \right. \\ &\quad \left. + r_3 u_3^2 + r_4 u_4^2 + r_5 u_5^2 \right) - \lambda_1 \left(\beta x_1 x_3 \right. \\ &\quad \left. + \beta x_1 x_4 + \alpha_{15} x_1 - \alpha_{51} x_5 + \gamma_1 x_1 u_1 \right. \\ &\quad \left. - \gamma_4 x_5 u_4 + \delta_1 x_1 - \mu_1 \right) + \lambda_2 \left(\gamma_1 x_1 u_1 \right. \\ &\quad \left. + \gamma_2 x_3 u_2 + \gamma_3 x_4 u_3 - \delta_2 x_2 + \mu_2 \right) \\ &\quad + \lambda_3 \left(\beta x_1 x_3 + \beta x_1 x_4 - \alpha_{34} x_3 - \gamma_2 x_3 u_2 \right. \\ &\quad \left. - \delta_3 x_3 + \mu_3 \right) + \lambda_4 \left(\alpha_{34} x_3 + \beta x_4 x_5 \right. \\ &\quad \left. + \beta x_3 x_5 - \gamma_3 x_4 u_3 - \delta_4 x_4 + \mu_4 \right) \\ &\quad + \lambda_5 \left(\alpha_{15} x_1 - \alpha_{51} x_5 - \beta x_4 x_5 - \beta x_3 x_5 \right. \\ &\quad \left. - \gamma_4 x_5 u_4 - \delta_5 x_5 + \mu_5 \right) \end{aligned} \tag{4}$$

The Hamiltonian function is constantly equal to zero along the optimal trajectories over the whole control interval, since the final time t_f is fixed. The necessary conditions for the costate $\lambda \in R^5$ are $\dot{\lambda}_i = -\frac{\partial H}{\partial x_i}$, $i = 1, \ldots, 5$, which give

$$\begin{aligned} \dot{\lambda}_1 &= \beta \lambda_1 x_3 + \beta \lambda_1 x_4 + \alpha_{15} \lambda_1 + \gamma_1 \lambda_1 u_1 \\ &\quad + \delta_1 \lambda_1 - \gamma_1 \lambda_2 u_1 - \beta \lambda_3 x_3 - \beta \lambda_3 x_4 \\ &\quad - \alpha_{15} \lambda_5 - \beta \lambda_3 x_3 - \beta \lambda_3 x_4 - \alpha_{15} \lambda_5 \end{aligned} \tag{5}$$

$$\dot{\lambda}_2 = \delta_2 \lambda_2 \tag{6}$$

$$\begin{aligned} \dot{\lambda}_3 &= -q_3 x_3 + \beta x_1 \lambda_1 - \gamma_2 \lambda_2 u_2 + \beta x_1 \lambda_3 \\ &\quad + \alpha_{34} \lambda_3 + \gamma_2 \lambda_3 u_2 + \delta_3 \lambda_3 - \alpha_{34} \lambda_4 \\ &\quad - \beta \lambda_4 x_5 + \beta \lambda_5 x_5 \end{aligned} \tag{7}$$

$$\begin{aligned} \dot{\lambda}_4 &= -q_4 x_4 + \beta x_1 \lambda_1 - \gamma_3 \lambda_2 u_3 - \beta x_1 \lambda_3 \\ &\quad - \beta \lambda_4 x_5 + \gamma_3 \lambda_4 u_3 + \delta_4 \lambda_4 + \beta \lambda_5 x_5 \end{aligned} \tag{8}$$

$$\begin{aligned} \dot{\lambda}_5 &= -q_5 x_5 - \alpha_{51} \lambda_1 - \gamma_4 \lambda_1 u_4 - \beta x_4 \lambda_4 \\ &\quad - \beta x_3 \lambda_4 + \alpha_{51} \lambda_5 + \beta x_4 \lambda_5 + \beta x_3 \lambda_5 \\ &\quad + \gamma_4 \lambda_5 u_4 + \delta_5 \lambda_5 \end{aligned} \tag{9}$$

for which $\lambda_i(t_f) = 0$, $i = 1 \ldots, 5$, hold since $x(t_f)$ is not fixed, while for the control u they are

$$0 = \frac{\partial H}{\partial u_1} = r_1 u_1 - \gamma_1 \lambda_1 x_1 \tag{10}$$

$$0 = \frac{\partial H}{\partial u_2} = r_2 u_2 - \gamma_2 \lambda_3 x_3 \tag{11}$$

$$0 = \frac{\partial H}{\partial u_3} = r_3 u_3 + \gamma_3 \lambda_2 x_4 - \gamma_3 \lambda_4 x_4 \tag{12}$$

$$0 = \frac{\partial H}{\partial u_4} = r_4 u_4 - \gamma_4 \lambda_1 x_5 - \gamma_4 \lambda_5 x_5 \tag{13}$$

From (10)–(13) the expressions for the controls are

$$u_1 = \frac{\gamma_1}{r_1} \lambda_1 x_1 \qquad u_2 = \frac{\gamma_2}{r_2} \lambda_3 x_2$$

$$u_3 = -\frac{\gamma_3}{r_3} \left(\lambda_2 - \lambda_4 \right) x_4 \quad u_4 = -\frac{\gamma_4}{r_4} \left(\lambda_1 - \lambda_5 \right) x_5$$

for which it is necessary to compute $x(t)$ and $\lambda(t)$, from $t = t_0$ to $t = t_f$, making use of equations (1), to be integrated from $x(t_0) = x_0$, and equations (5)–(9) to be integrated backwardly from $\lambda_i(t_f) = 0$, $i = 1, 2, 3, 4$.

IV. Simulations results

In this Section the results of some simulations are reported; the optimal control problem has been solved numerically. More precisely, the algorithm adopted is based on a sequential quadratic programming method: at each iteration a quadratic programming subproblem is solved by using a quasi-Newton approximation of the Hessian of the Lagrangian function. Different cases have been considered both to highlight the consistency of the model firstly introduced herein and to verify the effectiveness of the optimal control problem formulated in Section III. For the numerical simulations, the following values of the parameters are used: $\beta = 0.01$ for the infection rate; $\alpha_{15} = \alpha_{34} = 0.1$ for the contract rates of the second pathology; $\alpha_{51} = \alpha_{43} = 0.05$ for the recovery, with the hypothesis that it is easier to become ill than to recover. Moreover, without particular assumption, the same effectiveness of all the control actions has been chosen, and then $\gamma_i = 1$, $i = 1, 2, 3, 4$, whereas different death rates have been considered, taking $\delta_1 = \delta_2 = \delta_5 = 0.05$, $\delta_3 = 0.2$, $\delta_4 = 0.5$. Finally, the newcomers for all the groups, μ_i, $i = 1, \ldots, 5$ are assumed equal to 10. The choice of these numerical values has been guided by similarity with respect to classical epidemic models, such as the SIR one.

The initial conditions assumed reflect the situation in which the population is mostly composed by susceptible subjects and a small number of infected individuals. Then, they are set as $x_1(0) = 1000$, $x_2(0) = 0$, $x_3(0) = 10$, $x_4(0) = 0$ and $x_5(0) = 0$. All the control weights in the cost function (2) are initially set equal to $r_1 = r_2 = r_3 = r_4 = 10$. The term $x^T Q x$ in (2) is referred to the number of dead individuals among the three groups of patients. Then, each term $q_i x_i^2$ should correspond to such a number; the result is obtained setting $q_i = \delta_i^2$, $i = 3, 4, 5$.

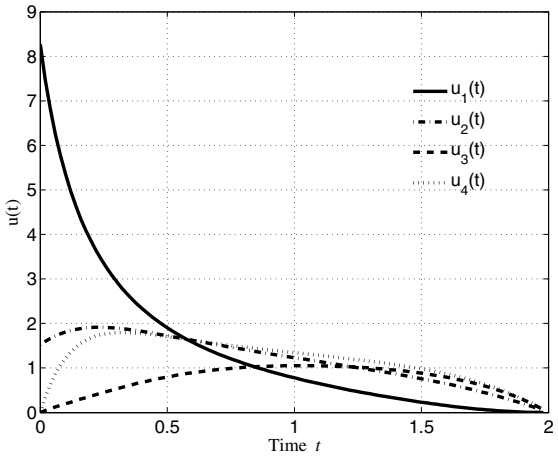

Fig. 2. The optimal controls.

A. Optimal control solution

To study the effectiveness of the model as well as the reasonability of the optimal control strategy, a first analysis is performed assigning the same weight to all the control in the cost index; as depicted in Figure 2, this brings to a strong vaccination action at the beginning, as it is reasonable expected, with the other actions becoming progressively more effective.

The overall obtained control strategy implies a significant decrease in the number of subjects in the x_3 , x_4 classes, and, in a smaller percentage, also in the x_1 class. The number of subjects immune from the first dangerous disease, the x_2 ones, increases, as well as those with only the second illness, the x_5 subjects. In Table I it is reported, for each class, an evaluation of the differences P_i, $i = 1, .., 5$ between the number of subjects under the obtained control actions of Figure 2 and the corresponding values of the uncontrolled cases, normalized with respect to the total number of subjects in the non controlled case, evaluated in the same instants. In particular the values are considered with a time step of three months, from the beginning of the control period to the end fixed at 2 years.

TABLE I
COMPARISON

$Time$ $months$	P_1 (%)	P_2(%)	P_3(%)	P_4 (%)	P_5(%)
0	0	0	0	0	0
3	-63.7	73.2	-8.1	-0.19	-1.13
6	-31	85.7	-50	-2.4	-1.1
9	2.1	92.2	-83.79	-6.5	0.58
12	5.2	97.9	-86.17	-8.84	0.9
15	5.1	102.6	-85.5	-10.6	0.96
18	4.9	107	-82.4	-12.2	1.0
21	4.98	111.4	-80.2	-13.	1.117
24	5	114.6	-78.2	-14.6	1.13

The results are reasonable, since the application of the vaccine control and/or the recovery from the x_3 and the x_4 classes implies the permanent immunity, and therefore the increase of the other two classes, the x_2 and the x_5. Also the number of subjects in the x_1 class, after a strong decrease up to month 6, increases, being less frequent the infectious contacts with patients in x_3 and x_4 classes.

B. The vaccination effects

The first choice already discussed of the weights in the cost index, while being useful for studying the model, does not take into account some reasonable considerations, to be applied especially in case of resource limitations. For example, it is obvious that the role of vaccination is significantly different from the one of medication on the subjects in the x_5 class and deserves a predominant study in this analysis; therefore from now on the control u_4 has been assumed equal to zero. Moreover, the effects of different choices for γ_1 have been studied, using the values $1, 0.8, 0.6, 0.5$. The parameter $\gamma_1 = 1$ means that the total effect is obtained, whereas $\gamma_1 = 0.5$ means that the vaccine reaches only 50% of the efficacy. This analysis can be used also to evaluate the behaviour of the epidemic disease corresponding to a refusal of vaccination prevention among the population.

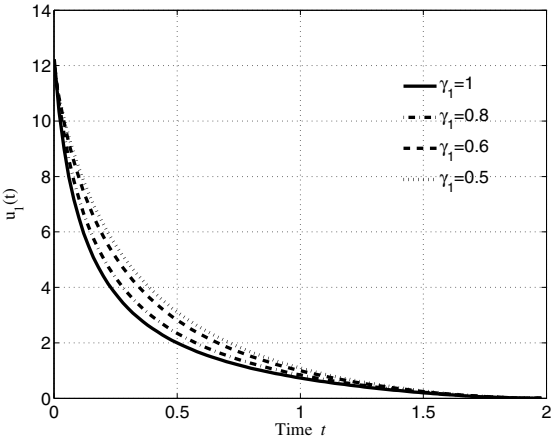

Fig. 3. $u_1(t)$ for different values of γ_1.

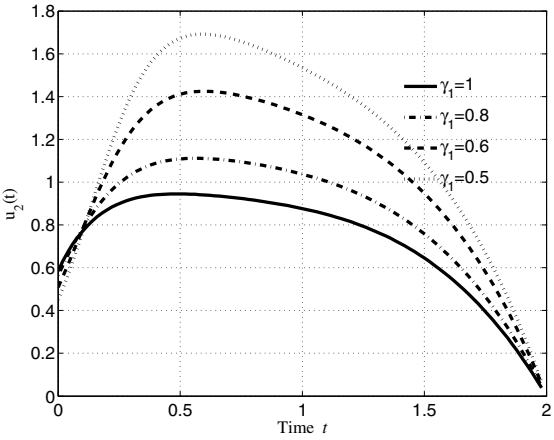

Fig. 4. $u_2(t)$ for different values of γ_1.

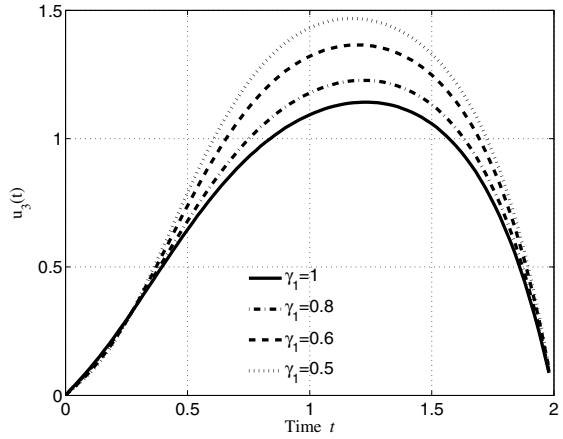

Fig. 5. $u_3(t)$ for different values of γ_1.

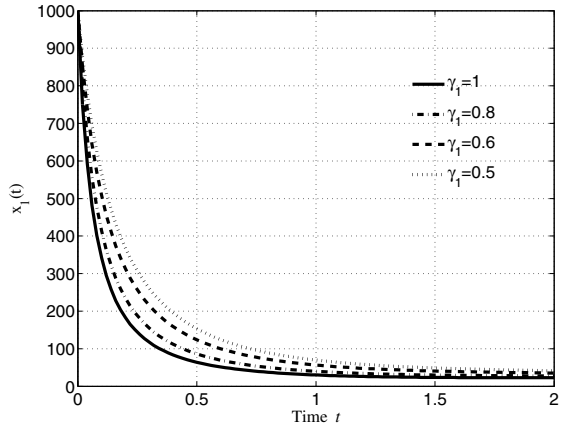

Fig. 6. $x_1(t)$ for different values of γ_1.

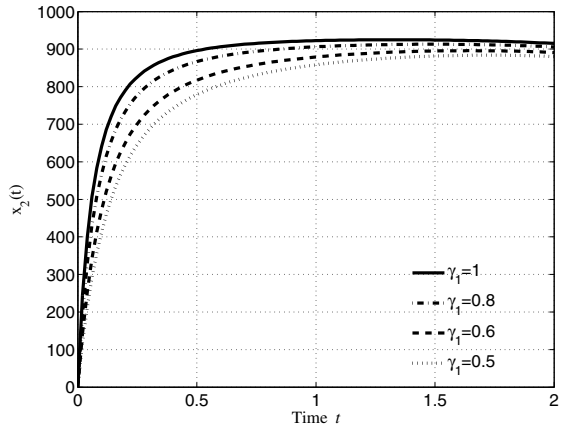

Fig. 7. $x_2(t)$ for different values of γ_1.

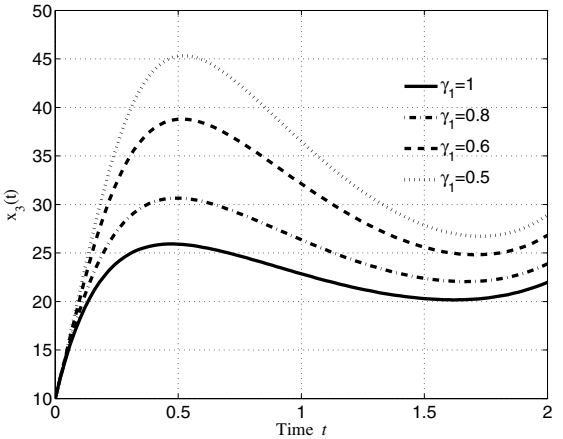

Fig. 8. $x_3(t)$ for different values of γ_1.

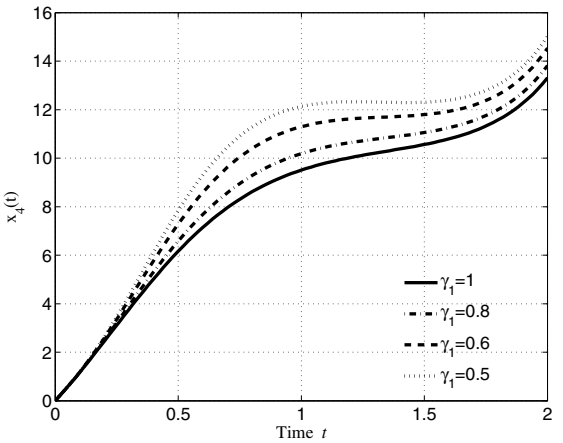

Fig. 9. $x_4(t)$ for different values of γ_1.

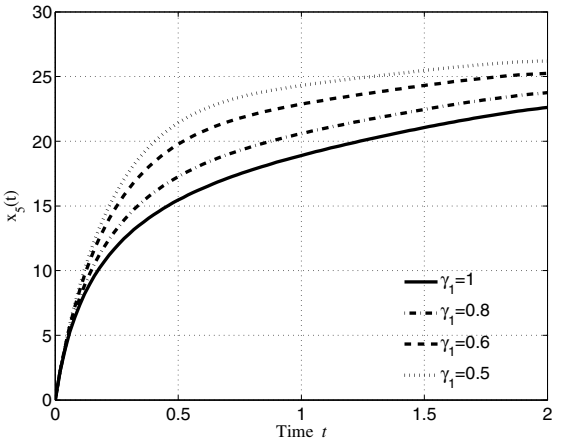

Fig. 10. $x_5(t)$ for different values of γ_1.

In Figure 3 it is shown that with a lower value of γ_1 it is required a slight increment in the necessity of vaccination u_1, and higher levels of therapy u_2 and u_3, as in Figures 4 and 5, respectively. The individuals behaviour is consequently affected by an higher number of subjects getting ill, both in the x_3 and in the x_4 class, as reported in Figure 8, 9 and 10. The number of subjects $x_1(t)$ decreases as γ_1 increases and, consequently, $x_2(t)$ reaches more rapidly higher values, as shown in Figures 6 and 7 respectively.

C. The control weights contribution

To investigate the influence of the choice of the weights in the cost index, Table II and Table III are displayed. To

characterise the effects of a control strategy in contrasting the two contemporary diseases considered in this case, the number of dead people in the categories of the ill subjects, the x_3, x_4 and x_5, is reported, with the idea that the more an intervention is effective, the lower is the number of people which die. This analysis is reported in Table II, with the results of the simulations for all the possible combinations of high (100) and low (10) values for the control weights r_i, $i = 1, 2, 3$. The number of dead individuals has been computed evaluating the time integral of each $x_i(t)$ over the control time $[0, 2]$ years, for each class separately and for their sum. At the same time, also the strength of the corresponding controls has been evaluated, in order to compare the different costs. These values are reported in Table III, where, for the same combination of weights as in Table II, the integrals of the control actions are computed, along with with their sum. It can be observed the importance of the control u_1: when a lower cost ($r_1 = 10$) is associated to u_1 in the cost function, its amplitude can increase and this implies a sensible reduction of the total number of dead patients; the four lower numbers of total diseased dead in Table II, first five rows, correspond to the case of $r_1 = 10$. These results are obtained with total costs substantially comparable, with a different distribution among each input cost, as evident in Table III. The higher number of dead people occurs when all the controls are "expensive" with respect to the number of patients x_i, $i = 3, 4, 5$ that could die for the two diseases, see the last three rows of Table II. It is also interesting to note the significant number of people dying for complication, dead in x_4, that is comparable with the one of those dying for the dangerous infectious disease. This furtherly justifies the interest of this study. From the control point of view, obviously the minor cost is obtained when the weights r_i, $i = 1, 2, 3$ are high, last row of III; what is interesting is to note that the second lower value of the cost, 54.2, is obtained with control actions that assure also the second lower value of the number of dead patients, 1028, second row od II. This means that an efficient resource allocations could guaranteed satisfactory results both from the patients point of view and from the $economic$ one.

TABLE II
DEAD.

Weights r_1, r_2, r_3	**Dead in** x_3	**Dead in** x_4	**Dead in** x_5	**Total diseased dead**
10, 10, 10	446	414	88	948
10, 10, 100	397	544	87	1028
10, 100, 10	596	425	79	1100
10, 100, 100	562	576	77	1215
100, 10, 10	886	573	126	1585
100, 100, 10	1100	546	103	1749
100, 10, 100	775	795	125	1695
100, 100, 100	1025	794	101	1920

V. CONCLUSIONS

In this paper it is proposed a model that analyses a population in which two diseases are present. More precisely, one disease is infectious; the other one is not infectious and not really dangerous by itself but could become mortal if it comes together with the first disease, as a complication. The topic is intriguing for different reasons; first, there are many diseases, like the HIV/AIDS or the hepatitis, that debilitates the patient's body that becomes so vulnerable to other diseases, even to light ailments, that can become fatal. The second reason concerns the elderly population who are invited to get vaccinated to avoid the flu, for example, and consequently also to avoid complications that together with the main epidemic can be mortal. The study proposed in this paper confirms the importance of an efficient resources allocation that could yield a decrease in the number of dead patients with a contextual efficient cost distribution. Future developments include the application of the model to case studies that could suggest different interactions and control strategies.

TABLE III
CONTROL COST.

Weights r_1, r_2, r_3	**Cost of** u_1	**Cost of** u_2	**Cost of** u_3	**Total cost**
10, 10, 10	32.99	14.70	15.06	62.76
10, 10, 100	33.66	16.46	3.90	54.02
10, 100, 10	35.10	5.00	16.80	56.90
10, 100, 100	35.87	5.38	4.51	45.76
100, 10, 10	15.73	34.04	22.68	72.45
100, 100, 10	20.11	15.51	25.71	61.33
100, 10, 100	16.82	35.64	7.53	59.99
100, 100, 100	20.94	15.74	8.25	44.93

REFERENCES

[1] T.K.Dasaklis, C.P.Pappis, and N.P.Rachanotis, "Epidemics control and logistic operations: a review," *Int. J. Production Economics*, 2012.

[2] H. Behncke, "Optimal control of deterministic epidemics," *Optimal control applications and methods*, vol. 21, 2000.

[3] P. Di Giamberardino, L. Compagnucci, C. D. Giorgi, and D. Iacoviello, "Modeling the effects of prevention and early diagnosis on hiv/aids infection diffusion," *IEEE Transactions on Systems, Man, and Cybernetics: Systems*, in Press, available on–line.

[4] P. Di Giamberardino and D. Iacoviello, "Hiv infection control: A constructive algorithm for a state-based switching control," *Int. Journal of Control, Automation and Systems*, vol. 16, no. 3, pp. 1469–1473, 2018.

[5] P. D. Giamberardino and D. Iacoviello, "LQ control design for the containment of the hiv/aids diffusion," *Control Engineering Practice*, vol. 77, pp. 162 – 173, 2018.

[6] A.C.Tsai, E.Mendenhall, J.A.Trostle, and I. Kawachi, "Co-occurring epidemics, syndemics and population health," *Lancet*, 2017.

[7] I.H.I.Ahmed, P. J.Witbooi, and K.Patidar, "Modeling the dynamics of an epidemic under vaccination in two interacting populations," *Journal of applied mathematics*, 2012.

[8] R.E.Rowthorn, R.Laxminarayan, and C.A.Gilligan, "Optimal control of epidemics in metapopulations," *J.Sol. Interface*, 2009.

[9] M.E.J.Newman and C.R.Ferrario, "Interacting epidemics and coinfection on contact networks," *PLOS ONE*, 2009.

[10] K. E. Dooley and R. E. Chaisson, "Tuberculosis and diabetes mellitus: convergence of two epidemics," *Lancet Infect Dis.*, 2010.

[11] T. O. A. B. Sutiono, H. Suwa, "Multi agent based simulation for typhoid fever with complications: an epidemic analysis," *51st Annual Meeting of the International Society for the Systems Sciences*, 2007.

[12] P. Di Giamberardino and D. Iacoviello, "Optimal control of SIR epidemic model with state dependent switching cost index," *Biomedical Signal Processing and Control*, vol. 31, 2017.