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Optimal Treatment Rate During an Influenza Pandemic in the Presence of Drug-Resistance Emergence

Problem Presenter: Seyed Moghadas (National Research Council, Institute for Biodiagnostics)

Academic Participants: Julien Arino (University of Manitoba), Huaxiong Huang (York University), Zanin Kavazovic (Université Laval), Roman Khaykin (York University), Brendan Pass (University of Toronto), Mohammad Sabbagh (Isfahan University of Tech.), Naveen Vaidya (York University).

Report prepared by: Julien Arino[1]

1 Introduction

The problem was posed by Seyed Moghadas, from the National Research Council Institute for Biodiagnostics in Winnipeg, Manitoba. It concerns the optimization of the rate of treatment with antivirals during a pandemic of influenza, to achieve the following objectives:

1. Minimize the total number of deaths due to influenza.
2. Minimize the total number of infections with influenza.
3. Reduce the spread of resistance to antivirals.

It is understood that not all the objectives above might be satisfied at the same time, and the purpose of the work is to consider the outcome in the different scenarios.

Antivirals generally target specific proteins on or in the virus and deactivate them, thereby suppressing the ability of the viruses to reproduce or infect target cells. Typically, they result in a reduction of the duration of symptoms and, in the case of influenza, prevent or attenuate some of the complications resulting from infection with the virus. Some antivirals can also be used in a prophylactic capacity, and may prevent infections arising in uninfected individuals.

The use of antivirals can therefore greatly alleviate the impact of an epidemic, by reducing the period of infectivity and by reducing the mortality associated to the epidemic.

However, the indiscriminate use of antivirals in recent years has had an adverse effect. A well known antiviral for influenza, oseltamivir (Tamiflu), was first shown to induce resistance in some of the circulating viral strains [7]. Such resistance has also been observed in other

[1] arinoj@cc.umanitoba.ca

types of antivirals, such as adamantane [8]. In the October-December 2005 period, 193 of 209 (92.3%) isolates of H3N2 human influenza virus in the United States tested positive for resistance to a certain type of antivirals (M2-inhibitors) [4].

Resistance has several correlated effects. Firstly, because it does not stop the viral progression in the host, it does not avert the adverse effects of influenza, and hence does not contribute to a reduction of mortality. Secondly, as it does not reduce the period of infectivity, it does not reduce the probability of new infections and thus has no effect on the control of the disease. Thirdly, because identifying the strain an individual bears requires lengthy and costly procedures, antivirals may be provided to individuals who are infected with a resistant strain, which amounts to a waste of resources since antivirals are useless on such individuals [2].

In these circumstances, while it is desirable to use antivirals, their use must also be conducted in a reasonable fashion, so as to avoid as much as possible the emergence of resistant strains[5, 6]. The aim of the present project is to see if optimal control theory can contribute to a better formulation of the treatment intensity, in order to bring the epidemic under control while avoiding wide-spread resistance in the population.

2 The model

We assume that the model takes the form shown in Figure 1. Starting as susceptible (S), individuals can then become infected with either the sensitive strain or with the resistant strain. Infection by the sensitive strain occurs when a susceptible has an infecting contact with either an untreated (I_U) or a treated (I_T) individual bearing the sensitive strain. Infection with the resistant strain occurs through contact with either an untreated (I_R) or a treated (I_W) individual bearer of the resistant strain. In both cases, it is assumed that upon infection, a susceptible enters the untreated (sensitive or resistant) class.

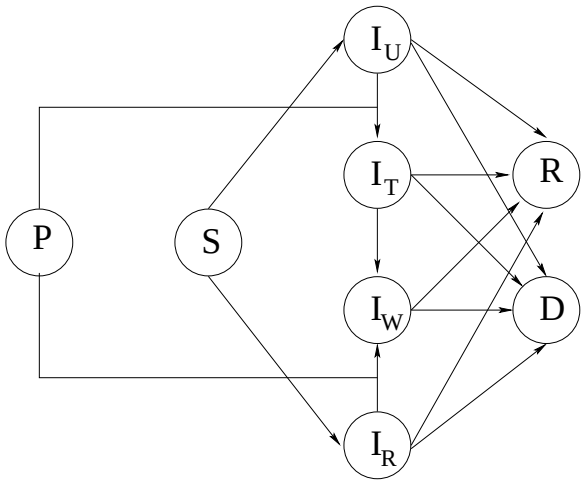

Figure 1 Flow chart illustrating the structure of the model.

An individual entering the untreated sensitive class I_U has several possibilities. He can become treated, at the per capita rate u, in which case he progresses to the I_T class. He can recover, at the per capita rate γ_U, or he can die, at the per capita rate d_U. A treated individual with the sensitive strain can also either recover or die at the per capita rates γ_T

and d_T, respectively. But the treatment can also cause the apparition of resistance. This happens at the per capita rate r. Evolving resistance means that the individual progresses to the class I_W of treated individuals who have the resistant strain.

The other route to the I_W class is through direct infection by a bearer of the resistant strain. Upon infection, a susceptible infected by the resistant strain progresses to the I_R class, where, similarly to what happens with the sensitive strain, he can be treated, recover or die at the per capita rates u, γ_R and d_R, respectively. Treatment of individuals in the I_W class constitutes a waste of drugs, since they have no effect on the resistant strain. Hence individuals in the I_W class have the same recovery and death rates as those in the I_R class.

The classes R and D are used to count individuals who have recovered or died from the disease, respectively. Lastly, the P class represents the number of new courses of treatment that are available at time t, that is, how many new infected individuals can be treated.

We consider the system

$$S' = -(\beta_U I_U + \beta_T I_T + \beta_R(I_R + I_W))S \tag{2.1a}$$
$$I_U' = (\beta_U I_U + \beta_T I_T)S - (u + \gamma_U + d_U)I_U \tag{2.1b}$$
$$I_T' = uI_U - (d_T + \gamma_T + r)I_T \tag{2.1c}$$
$$I_R' = \beta_R(I_R + I_W)S - (u + \gamma_R + d_R)I_R \tag{2.1d}$$
$$I_W' = uI_R + rI_T - (\gamma_R + d_R)I_W \tag{2.1e}$$
$$R' = \gamma_U I_U + \gamma_T I_T + \gamma_R(I_R + I_W) \tag{2.1f}$$
$$D' = d_U I_U + d_T I_T + d_R(I_R + I_W) \tag{2.1g}$$
$$P' = -u(I_U + I_R), \tag{2.1h}$$

with initial conditions $S(0) = S_0 > 0$, $I_U = I_0 \geq 0$, $I_T = I_R = I_W = R = D = 0$ and $P(0) = \Delta \geq 0$. The initial condition Δ represents the total number of courses of treatment that can be initiated at time $t = 0$.

3 Optimal control

We will make use of the Pontryagin maximum principle. We recall here the general principles of this approach (see, e.g., [1, 3]). Given an initial value problem

$$x' = f(t, x(t), u(t)), \quad x(t_0) = x_0, \tag{3.1}$$

one defines a *cost functional*

$$J = \int_{t_0}^{T} F(t, x(t), u)dt \tag{3.2}$$

to be minimized. The function $u(t)$ is the *control*. Note that here we consider finite-time control, in the sense that the solution to (3.1) is considered only on the interval $[0, T]$. The form (3.2) is not the most general, but corresponds to what will be used later. Such a functional defines a *Lagrange problem*. Other forms are those where the cost function only depends on the trajectory at the terminal moment T (*Mayer problem*) or a combination of Lagrange and Mayer problems (*Boltz problem*).

Our aim will be to minimize J (using admissible values of u), not to obtain a prescribed end state of the system. Our problem is thus one with variable end point and fixed time. The following result holds [1], which we state in its classical form involving a maximum.

Theorem 3.1 (Pontryagin maximum principle) *Let $u_0(t)$ be the optimal control in the problem*

$$\begin{aligned} x' &= f(t, x(t), u(t)), \quad x \in \mathbb{R}^n, u \in \mathbb{R}^m, t_0 \le t \le T, \quad x(t_0) = x_0 \\ J(u) &= \phi(x(T)) \to \mathit{inf}, \\ u(t) &\in U \end{aligned}$$

and $x_0(t)$ be the corresponding optimal trajectory. Then $u_0(t)$ satisfies the maximum condition

$$\max_{u \in U} H(t, x_0(t), u, \psi(t)) = H(t, x_0(t), u_0(t), \psi(t)). \tag{3.3}$$

The Hamiltonian is determined by the expression

$$H(t, x(t), u(t), \psi(t)) = \psi'(t) f(t, x(t), u(t)),$$

and the adjoint variables $\psi(t)$ are solutions of the problem

$$\psi'(t) = -H_x(t, x_0(t), u_0(t), \psi(t)) \quad \psi(T) = -\phi_x(x_0(T)).$$

We will see in the following sections how this result is applied to our system.

3.1 Cost functional used. We use

$$\min_{0 \le u(t) \le \bar{u}} \int_0^T \mathcal{L}\, ds, \tag{3.4}$$

where

$$\mathcal{L} := D'(s) + \varepsilon u(s)^2 (I_U(s) + I_R(s)) \tag{3.5}$$

under the constraint that

$$P(T) \ge 0. \tag{3.6}$$

The functional (3.5) accounts for the number of deaths due to the disease as well as a cost of treatment. The quantity $\int_0^T D'(s) ds$ gives the total number of deaths over the time interval $[0, T]$. The cost of treatment is here assumed to be a quadratic function of the treatment rate u. Using this hypothesis enables to avoid a bang-bang control.

The value $\bar{u}$ is the maximal possible rate of treatment. It is a function of infrastructure. For example, the treatment rate might be limited by the number of healthcare workers able to administer it, or by the number of hospital beds available.

3.2 Hamiltonian and adjoint system. We form the Hamiltonian

$$\mathcal{H} := \lambda_1 S' + \lambda_2 I_U' + \lambda_3 I_T' + \lambda_4 I_R' + \lambda_5 I_W' + \lambda_6 R' + \lambda_7 D' + \lambda_8 P' + \mathcal{L}. \tag{3.7}$$

Solving $\partial \mathcal{H} / \partial u = 0$, we find that

$$u^* = \frac{(\lambda_2 - \lambda_3) I_U + (\lambda_4 - \lambda_5) I_R}{2\varepsilon (I_U + I_R)}. \tag{3.8}$$

It is here that the assumption of quadratic dependence on the treatment rate u made in (3.5) plays a role: if $\mathcal{L}$ depends linearly on u, then $\partial \mathcal{H} / \partial u = 0$ cannot be solved for u and we have to assume that $u^* = 0$ or $u = u^*$, that is, bang bang control.

To find the adjoint variables, we use $\lambda_i' = -\partial \mathcal{H} / \partial x_i$, where $x_i \in \{S, I_U, I_T, I_R, I_W, R, D, P\}$. We start by noticing that

$$\frac{\partial \mathcal{H}}{\partial R} = \frac{\partial \mathcal{H}}{\partial D} = \frac{\partial \mathcal{H}}{\partial P} = 0.$$

Since the terminal conditions are $\lambda_i(T) = 0$, it follows from uniqueness of solutions that $\lambda_6 \equiv \lambda_7 \equiv \lambda_8 \equiv 0$. Using this fact, we find the dynamics of the other adjoint variables to be given by

$$\lambda_1' = (\beta_U I_U + \beta_T I_T)(\lambda_1 - \lambda_2) + \beta_R(I_R + I_W)(\lambda_1 - \lambda_4) \tag{3.9a}$$

$$\lambda_2' = \beta_U S(\lambda_1 - \lambda_2) + (u^* + \gamma_U + d_U)\lambda_2 - u^*\lambda_3 - d_U - \varepsilon {u^*}^2 \tag{3.9b}$$

$$\lambda_3' = \beta_T S(\lambda_1 - \lambda_2) + (d_T + \gamma_T + r)\lambda_3 - r\lambda_5 - d_T \tag{3.9c}$$

$$\lambda_4' = \beta_R S(\lambda_1 - \lambda_4) + (u^* + \gamma_R + d_R)\lambda_4 - u^*\lambda_5 - d_R - \varepsilon {u^*}^2 \tag{3.9d}$$

$$\lambda_5' = \beta_R S(\lambda_1 - \lambda_4) + (\gamma_R + d_R)\lambda_5 - d_R, \tag{3.9e}$$

with u^* given by (3.8). System (3.9) is considered with terminal conditions $\lambda_i(T) = 0$.

3.3 Numerical solution of the problem. To explain the method used to construct numerical solutions to the optimal control problem, we let $x \in \mathbb{R}^8$ represent the state variables $\{S, I_U, I_T, I_R, I_W, R, D, P\}$ and $\Lambda \in \mathbb{R}^5$ represent the adjoint variables $\{\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5\}$. Systems (2.1) and (3.9) can then be written as

$$x' = f(x, \Lambda) \tag{3.10a}$$

$$\Lambda' = g(x, \Lambda) \tag{3.10b}$$

under the initial and terminal conditions

$$x(0) = \xi_0$$
$$\Lambda(T) = 0.$$

We construct a convergent sequence of approximations $(x_k(t), \Lambda_k(t))$ to the solution to this boundary value problem as follows.

1. Start with an initial guess solution $\Lambda_0(t)$ for $t \in [0, T]$. For example, $\Lambda_0(t) \equiv 0$ for $t \in [0, T]$.
2. Integrate (3.10a) from $t = 0$ to $t = T$, using $\Lambda_0(t)$ as a nonautonomous component and the initial condition $x(0) = \xi_0$. This gives $x_0(t)$.
3. Integrate (3.10b) backward in time from $t = T$ to $t = 0$, using the solution $x_k(t)$ as a nonautonomous component and the initial condition $\Lambda(T) = 0$. This gives $\Lambda_{k+1}(t)$.
4. Integrate (3.10a) from $t = 0$ to $t = T$, using the value of $\Lambda_{k+1}(t)$ found in step 3 as a nonautonomous component and the initial condition $x(0) = \xi_0$. This gives $x_{k+1}(t)$.
5. Repeat steps 3 and 4 until convergence.

3.4 Practical implementation of the algorithm. Some caution is required when using the algorithm presented above. Because of the nature of (3.8), the problem can be stiff when I_U and I_R become close to zero. As a consequence, it was necessary to use a stiff routine such as `ode15s`. Because adaptive step size routines produce by default values at time points that vary from iteration to iteration, we use the format

```
ode15s(@rhs_fct,[t0:tstep:tf],IC)
```

that allows to specify the time points at which output is to be produced. The main loop explained in the previous section can be carried out, in MATLAB, using the following simple loop:

```
[t,x]=ode15s(@rhs_state_eq,t_positive,IC_state,[],p);
p.x=[x,p.x(1:end,9:13)];
[t,x]=ode15s(@rhs_adjoint_eq,t_negative,IC_adjoint,[],p);
```

```
p.x=[p.x(1:end,1:8),flipud(x)];
```

Using this method and storing the result in the structure `p` allows to reduce the number of operations and the size in memory of the variables.

4 Numerical results

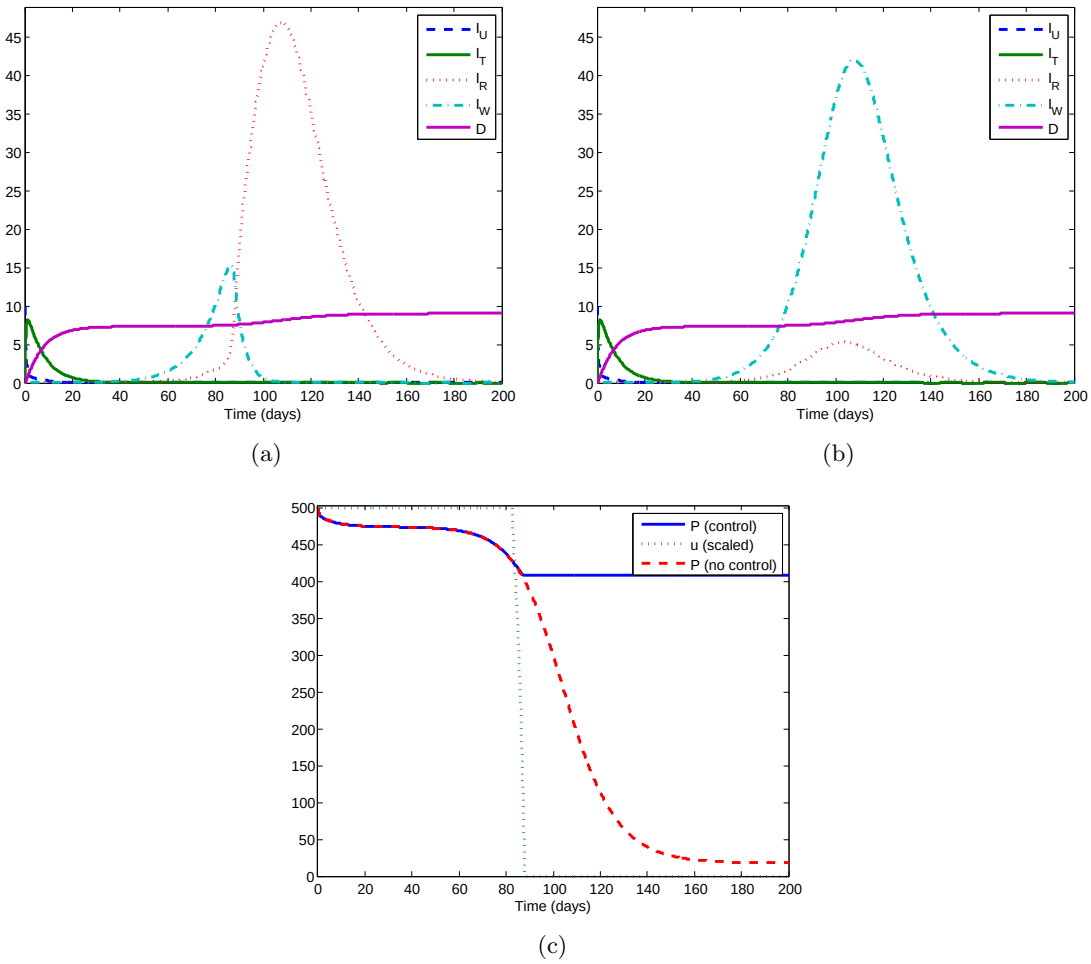

Figure 2 Situation with no run-out both in the optimally controlled and the constantly controlled cases, for a total population of 1000 individuals. (a) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, optimal control case. (b) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, constant control case. (c) Number of new infectious that be treated (P) in the optimal control and constant control (no control) cases, and scaled treatment rate (u) in the optimal control case.

In Figures 2 to 5, we display three items:

(a) The numbers of individuals in the different infected classes (I_U, I_T, I_R and I_W) as well as the cumulative number of deaths, as a function of time, in the case where the optimal control policy is applied.

(b) The same quantities, but in the case with no optimal control, that is, with a constant treatment rate applied as long as there remains some courses of treatment.

(c) The number of courses of treatment available as a function of time, in the case of optimal control (control) and constant treatment (no control). In the case with optimal control, the scaled treatment rate used as a function of time is also shown.

The figures are ordered by decreasing number of initially available courses of treatment, all other parameters and initial conditions being considered equal throughout simulations.

In Figure 2, there are initially resources for the treatment of 500 new infectives. This number is sufficient even when a constant treatment rate is applied. The effect of (3.5) is clearly visible. Figure 2(a)

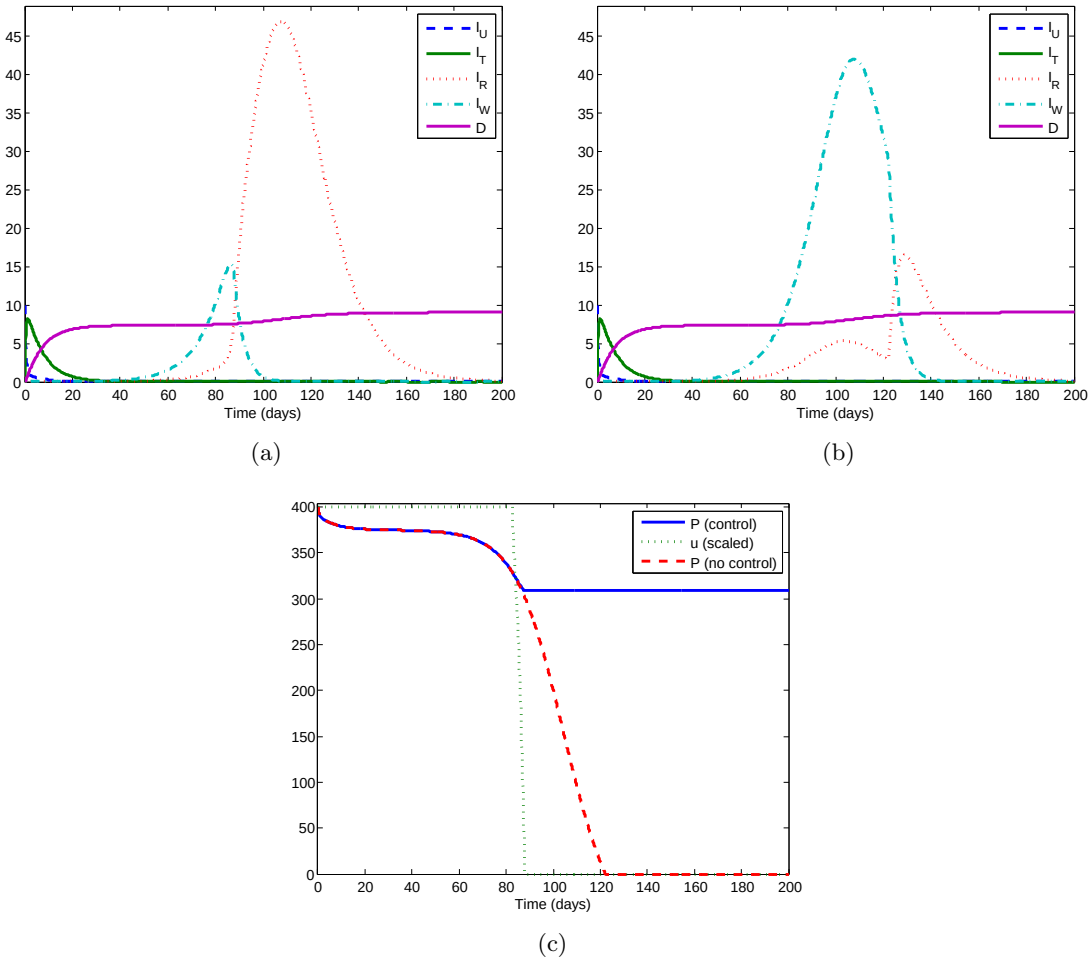

Figure 3 Situation with no run-out in the optimally controlled case and run-out in the constantly controlled case, for a total population of 1000 individuals. (a) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, optimal control case. (b) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, constant control case. (c) Number of new infectious that be treated (P) in the optimal control and constant control (no control) cases, and scaled treatment rate (u) in the optimal control case.

In Figure 3, there are initially enough courses of treatment when optimal control is used, but not enough in the case of constant treatment, where run-out occurs. Note that, interestingly, there is a second wave of resistant infection taking place after run-out, in the case where constant treatment is used.

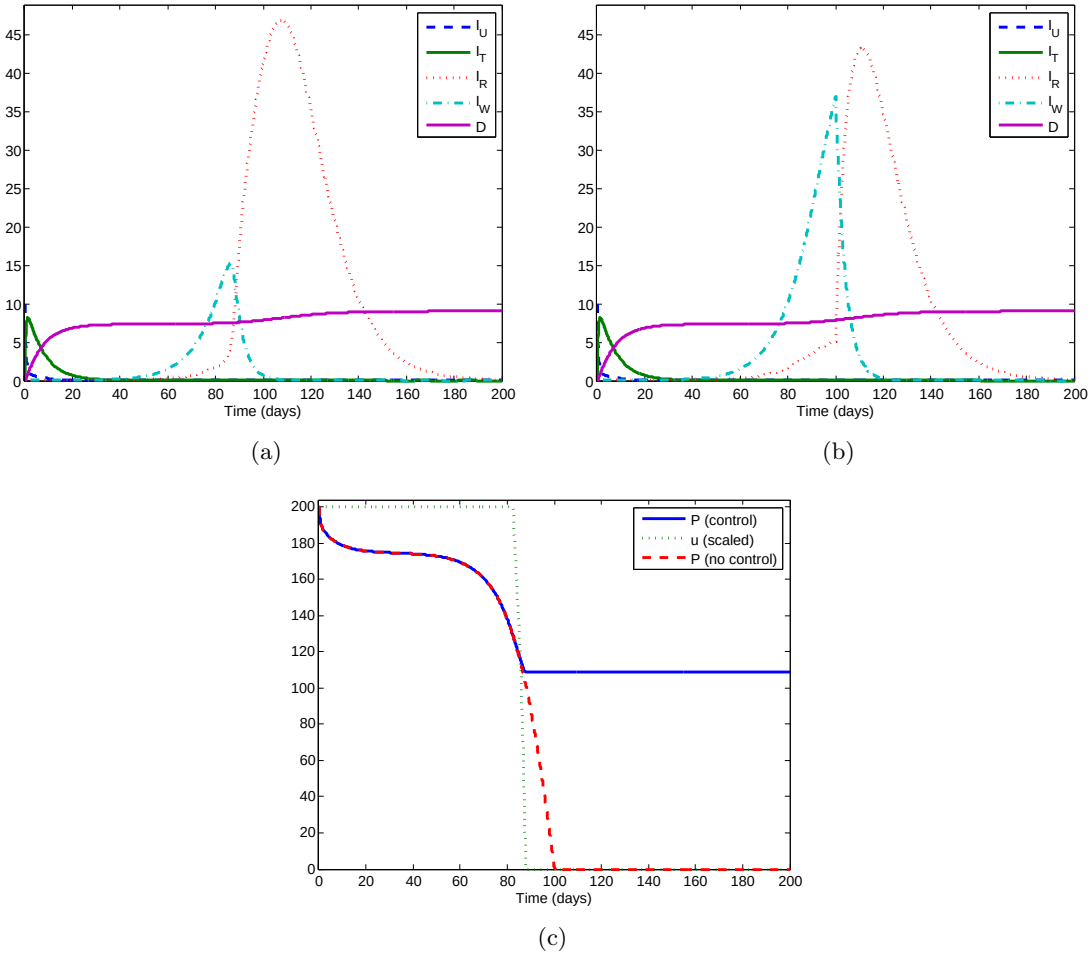

Figure 4 Situation with no run-out in the optimally controlled case and run-out in the constantly controlled case, for a total population of 1000 individuals. (a) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, optimal control case. (b) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, constant control case. (c) Number of new infectious that be treated (P) in the optimal control and constant control (no control) cases, and scaled treatment rate (u) in the optimal control case.

Figure 4 is very similar to Figure 3, with the difference that run-out occurs sooner in the uncontrolled case, so that the resistant infection is increasing at that time.

Note that in Figures 3 and 4, the optimal control policy consists in treating at the maximum rate (the same as in the uncontrolled case) until some time, then rapidly shutting off treatment, which is a sort of continuous version of bang bang control.

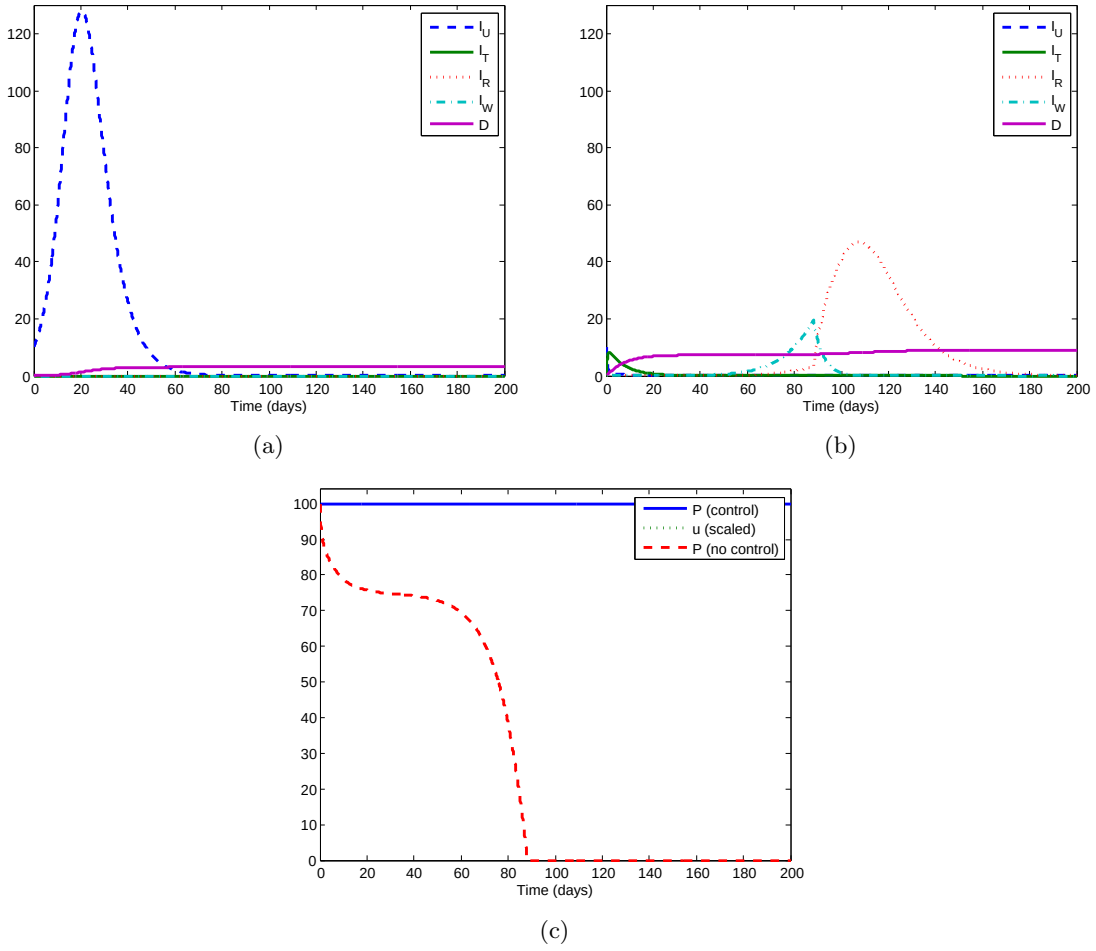

Figure 5 Situation with run-out both in the optimally controlled and the constantly controlled cases, for a total population of 1000 individuals. (a) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, optimal control case. (b) Numbers of infectious individuals in the various infectious classes, as well as cumulative number of deaths, constant control case. (c) Number of new infectious that be treated (P) in the optimal control and constant control (no control) cases, and scaled treatment rate (u) in the optimal control case.

5 Conclusion

Using a treatment rate obtained using optimal control theory seems an efficient way to mitigate the epidemic while avoiding the spread of resistance. The most striking feature of the optimal control approach is in its capacity to reduce the waste of antivirals, as seen when comparing, in Figures 2 to 5, the cases with and without optimal treatment.

Further work will be needed to explore more in detail the model and its conclusions. In particular, a comparison of optimization criteria (cost functionals) should be undertaken, to assure that the strategy deduced using optimal control does not depend too much on the nature of the functional.

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