A note on the use of optimal control on a discrete time model of influenza dynamics

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Abstract

A discrete time Susceptible - Asymptomatic - Infectious - Treated - Recovered (SAITR) model is introduced in the context of influenza. We evaluate the potential effect of control measures such as social distancing and antiviral treatment on the dynamics of a single outbreak. Optimal control theory is applied to identify the best way of reducing the number of infected and dead individuals, at a minimal cost. The problem is solved by using a discrete version of Pontryagin's maximum principle. Numerical results show that dual strategies have stronger impact in the reduction of the final epidemic size.

1 Introduction

In April of 2009 the World Health Organization (WHO) announced the emergence of a novel strain of A-H1N1 influenza. National and international public health agencies quickly took (often drastic) emergencies measures and in June of 2009, the World Health Organization (WHO) and US Centers for Disease Control (CDC) declared the outbreak to be a pandemic. Mathematical models are being used to evaluate the usefulness of the policies used during this pandemic.

For the last decade, continuous time models have been used to study single influenza outbreaks [Arino et al.(2003)Arino, Brauer, van den Driessche, Watmough, and Wu, Nuno et al.(2007)Nuno, Chowell, Wang, and Castillo-Chavez]. The identification of optimal control strategies involving antiviral treatment and the isolation of infectious individuals have been studied using continuous time models [Lee et al.(2010)Lee, Chowell, and Castillo-Chavez]. We proceed to identify optimal control policies aimed at minimizing the number of infected and dead individuals via the use of the most "cost-effective" policies involving "social distancing" and antiviral treatment within a discrete time epidemic framework that it is not just a discretization of a continuous-time model. Optimal control theory [Behncke(2000), Jung et al.(2005)Jung, Lenhart, Protopopescu, and C.,S. and J.(2007)] is the main approach used in our analysis.

The model's basic reproductive number is computed as well as final epidemic size relations (with and without controls). Only the implementation of intervention measures referred to as social distancing and antiviral treatment are explored in this note. Numerical simulations highlight the differences that result from the implementation of single versus dual intervention policies.

2 Discrete SAITR Model

The total population under consideration is divided into susceptible (S), asymptomatic (A), infectious (I), treated (T), recovered (R), and dead (D) (from influenza) classes of individuals. Births and deaths from natural causes are ignored since the focus is on single outbreaks. Treatment and social distancing are the only control policies explored in this note. The fraction of susceptible individuals at time t that remain susceptible at time $t+1$ is

modeled by the function

$$G_t = \exp\left(-\beta(1-x_t)\frac{I_t + mA_t + \rho T_t}{N_t}\right),$$

where N_t denotes the total population, β the transmission rate, and m and ρ $(0 < m, q \leq 1)$ the reductions in transmissibility for the asymptomatic and treated classes, respectively. The function x_t (control) models the reduction in the number of contacts per unit of time ("generation"). The fraction of individuals who get the disease but do not develop symptoms is given by q while δ denotes the proportion of disease-induced deaths per generation; the fraction of infected individuals who get treatment each generation is modeled by the function τ_t. It is assumed that asymptomatic and infectious individuals recover with probability σ_1 (per generation) while treated individuals recover with probability σ_2 (per generation). The model (with two controls) is given by the following system of nonlinear difference equations:

$$\begin{array}{rcl} S_{t+1} & = & S_t G_t \\ A_{t+1} & = & qS_t(1-G_t) + (1-\sigma_1)\,A_t \\ I_{t+1} & = & (1-q)S_t\,(1-G_t) + (1-\tau_t)\,(1-\sigma_1)\,(1-\delta)I_t \\ T_{t+1} & = & (1-\sigma_2)\,T_t + \tau_t\,(1-\sigma_1)\,(1-\delta)I_t \\ R_{t+1} & = & R_t + \sigma_1 A_t + \sigma_1\,(1-\delta)\,I_t + \sigma_2 T_t \\ D_{t+1} & = & D_t + \delta I_t. \end{array} \tag{1}$$

In the absence of controls ($x_t \equiv 0$ and $\tau_t \equiv 0$, for all t), the following final size relationship is derived

$$\ln\left(\frac{S_0}{S_\infty}\right) = R_0\left(1 - \frac{S_\infty}{N}\right) \tag{2}$$

following the approach in [Brauer et al.(2010)Brauer, Feng, and Castillo-Chavez]. The basic reproductive number R_0 in this case is

$$R_0 = \beta\left(\frac{(1-q)}{1-(1-\sigma_1)\,(1-\delta)} + m\frac{q}{\sigma_1}\right). \tag{3}$$

R_0 is a dimensionless quantity that accounts for the number of (initial) secondary cases generated by two classes: the infected (I) and the asymptomatic (A) in a population of primary susceptible individuals. The addition of controls replaces the expression in (2) by the inequality

$$\ln\left(\frac{S_0}{S_\infty}\right) \leq R_0\left(1 - \frac{S_\infty}{N}\right). \tag{4}$$

The following result is easily established.
Result 2.1: If S_∞ is a solution of (2) and S_∞^{wc} satisfy the inequality (4) then $S_\infty^{wc} \geq S_\infty$, that is, the use of controls reduces the final epidemic size. [An outline of the proof is found in Appendix B].

We observe that the fraction of the population that becomes infected during the course of a single epidemic outbreak in the absence of controls is $1 - \frac{S_\infty}{N}$ while the corresponding fraction with controls would be $1 - \frac{S_\infty^{wc}}{N}$. The final epidemic size decreases as a result of the implementation of social distancing measures or the application of alternative control measures. Numerical simulations that compute the final epidemic sizes with and without controls are used to corroborate Result (2.1).

3 Optimal control problem

Our goal is to minimize the number of infected and dead individuals via the judicious (cost effective) use of social distancing and antiviral treatment measures over the finite interval $[0, T_f]$. The objective functional $\mathcal{F}$ used to formulate the appropriate optimization problem is given by

$$\mathcal{F}(\mathbf{x}, \boldsymbol{\tau}) = \frac{1}{2} \sum_{t=0}^{T_f - 1} F(\mathbf{y}_t, x_t, \tau_t, t) \tag{5}$$

where

$$F(\mathbf{y}_t, x_t, \tau_t, t) = B_0 I_t^2 + B_1 D_t^2 + B_2 x_t^2 + B_3 \tau_t^2; \tag{6}$$

with $\mathbf{x} = (x_0, x_1, ..., x_{T_f - 1})$ and $\boldsymbol{\tau} = (\tau_0, \tau_1, ..., \tau_{T_f - 1})$ the control variables. Further $\mathbf{y} = (y_0, y_1, ..., y_{T_f})$ is the state variable with $\mathbf{y}_t = (S_t, A_t, I_t, T_t, R_t, D_t)^T$. The weight constants B_i, $(i = 0, 1, 2, 3)$ are a measure of the relative cost of interventions over $[0, T_f]$. The use of these definitions and notations lead to the problem of finding control functions $\mathbf{x}$ and $\boldsymbol{\tau}$ such that

$$\mathcal{F}(\mathbf{x}^*, \boldsymbol{\tau}^*) = \min_U \mathcal{F}(\mathbf{x}, \boldsymbol{\tau}), \tag{7}$$

where $U = \{(x_t, \tau_t) : 0 \leq x_t \leq x_{\max}, 0 \leq \tau_t \leq \tau_{\max}, t = 0, 1, ..T_f - 1\}$, subject to the state equations in Model (1) and appropriate initial condition. Three different strategies are compared:

- Strategy 1: Social distancing ($x_t \geq 0$, $\tau_t \equiv 0$),

- Strategy 2: Antiviral treatment ($\tau_t \geq 0$, $x_t \equiv 0$),
- Strategy 3: Antiviral treatment and social distancing.

The relative impact of these strategies is "evaluated" from their effect on the final size relations under single or dual policies. The optimization problem is solved by using a discrete version of Pontryagin's maximum principle [Hwang and Fan(1967), Jung et al.(2005)Jung, Lenhart, Protopopescu, and C., Pontryagin et al.(1962)Pontryagin, Boltyanskii, Gamkrelidze, and Mishchenko] (details are provided in Appendix C). The Hamiltonian associated with the problem is given by

$$H_t = F(\mathbf{y}_t, x_t, \tau_t, t) + \boldsymbol{\lambda}_{t+1}^T \mathbf{y}_{t+1}, \quad \text{for} \quad t = 0, 1, 2, .., T_f - 1, \tag{8}$$

where x_t, τ_t are the control variables, and $\mathbf{y}_t$ and $\boldsymbol{\lambda}_t \in \mathbb{R}^6$ are the state and adjoint variables, respectively. The adjoint equations are

$$\lambda_t^i = \frac{\partial H_t}{\partial y_t^i} \quad \text{for} \quad t = 0, 1, 2, .., T_f - 1, \quad i = 1, 2, ..., 6, \tag{9}$$

where λ_t^i and y_t^i are the i-th component of $\boldsymbol{\lambda}_t$ and $\mathbf{y}_t$, respectively. The problem is solved using the following forward-backward algorithm [S. and J.(2007)]:

- Step 1. Initial guess for $\mathbf{x}^0$, $\boldsymbol{\tau}^0$ and condition $\mathbf{y}_0$ are selected,
- Step 2. Solve State Equation (1) forward in time,
- Step 3. Solve Adjoint Equation (9) backward in time subject to the transversality conditions $\boldsymbol{\lambda}_{T_f} = 0$,
- Step 4. Solve the optimality conditions $\frac{\partial H_t}{\partial x_t} = 0$, $\frac{\partial H_t}{\partial \tau_t} = 0$,
- Step 5. Check convergence. That is, if $\frac{\|\mathbf{u} - \mathbf{u}_{old}\|}{\|\mathbf{u}\|} < 0.001$ for $\mathbf{u} \in \{\mathbf{x}, \boldsymbol{\tau}\}$ stop. If $\frac{\|\mathbf{u} - \mathbf{u}_{old}\|}{\|\mathbf{u}\|} \geq 0.001$ go to Step 2.

4 Numerical results

The results of selected simulations generated by the numerical implementation of the strategies described in Section 3 are discussed in this section. The numbers of infected individuals generated under low R_0 (1.3 - 1.8) or high R_0 (2.4 - 3.2) in the absence of controls or in the presence of single or dual optimal controls are compared. A sensitivity analysis is carried out on the robustness of these simulations in relationship to the values of a priori selected constraints on the ranges of the bounds on the controls x_t and τ_t [$x_t \in (0, 0.2)$, $\tau_t \in (0, 0.05)$]. The weight constants (B_2 and B_3) are the relative costs associated with the implementation of social distancing and antiviral treatment, respectively. The weight constants must be selected in part to facilitate computational issues. We found out that the numerical approach used to solve this discrete optimal control problem is sensitive to the weight constants on the controls. The sensitivity arises in part from the fact that all parameters in our discrete model represent daily rates, the time step being one day ($t \to t + 1$). Hence, we use small ranges for the weight constants in order to guarantee convergence to the optimal solutions ($B_2 \in [0.002, 0.2]$ and $B_3 \in [0.015, 1]$). For most of our simulations, we choose $B_2 = 0.004$ (social distancing as the base line value) and B_3 (antiviral treatment) which it is assumed to be approximately ten times larger than B_2 ($B_3 \cong 10B_2$).

4.1 Implication of social distancing and antiviral treatment

We compare the reduction in the final size and also the reduction in the proportion of daily infected cases that result from the implementation of Strategies 1, 2, and 3. For this simulation, the weight constants on the two controls are $B_2 = 0.004$ and $B_3 \cong 10B_2$. Results under two different values for R_0, a moderate value ($R_0 = 1.3$) and a high value ($R_0 = 2.4$) are displayed in Figure 1 and Figure 2, respectively. Figure 1A and Figure 2A show the optimal control solution for each strategy. Figures 1B, C and Figures 2B, C help compare the impact of each strategy on the cumulative proportion of infected individuals and the proportion of daily infected cases. Figure 1A shows that the optimal control solutions under social distancing and antiviral treatment use less than the maximum value permitted, within an outbreak that lasts almost 200 days, when R_0 is low ($R_0 = 1.3$).

In Figure 1B, dual policies generate strong reductions of almost 33% in

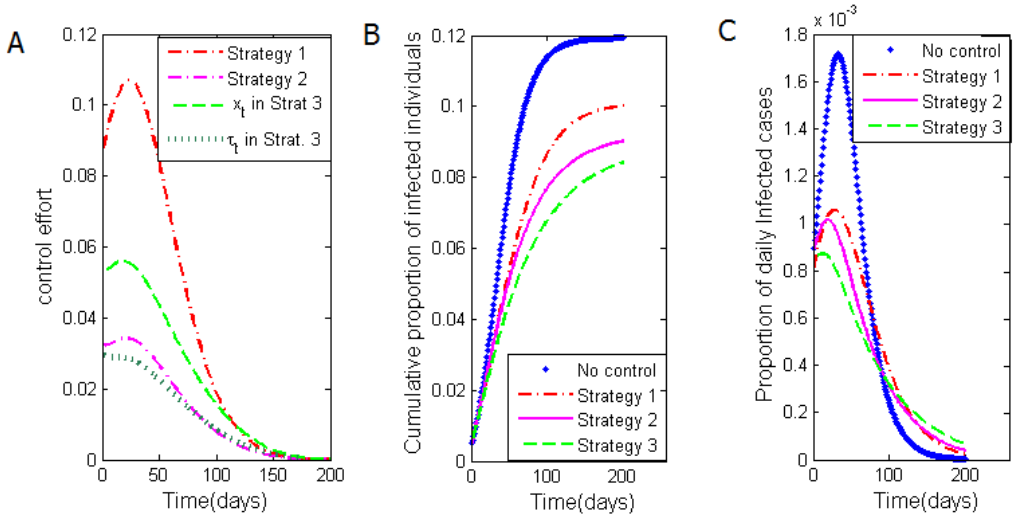

Figure 1: For a moderate value of $R_0 = 1.3$, the optimal control solution does not required the application of the permitted maximum values. However, there is a strong impact in the reduction of the final epidemic size by the application of each strategy. Strategy 3 has the most significant reduction, almost 32%

the final epidemic size as well as 16% reduction under Strategy 1, and 25% under Strategy 2. The epidemic peak is reduced also by almost 50% when dual policies are applied (Figure 1C). Figure 2 plots optimal controls and the resulting cumulative proportions of infected cases when $R_0 = 2.4$. The optimal control solution for each strategy requires the application of the maximum effort during the first 50 days. The curves in Figure 2B show that the epidemic ends within 100 days of the start of the outbreak. Strategy 3 yields the largest reduction in the final epidemic size, 22% but only an 8% reduction under Strategy 1, and an 11% reduction under Strategy 2.

The impact of optimal strategies in terms of the final size as a function of R_0 is presented in Figure 3. Under a single policy, for small R_0 (up to ~ 1.45), Strategy 2 is more effective in reducing the final epidemic size when compared to Strategy 1. However, the effect is reversed when $R_0 \geq 1.45$. A dual policy has the strongest impact in the reduction of the final epidemic size for all ranges of R_0 ($R_0 \in [1.3, 3.2]$ [Chowell et al.(2006)Chowell, Ammon, Hengartner, and Hyman,Chowell et al.(2007)Chowell, Nishiura, and Bettencourt, Mills et al.(2004)Mills, Robins, and Lipsitch]). Under higher

values of R_0 ($R_0 \geq 3$), no policy seems effective whenever the goal is to reduce the final epidemic size.

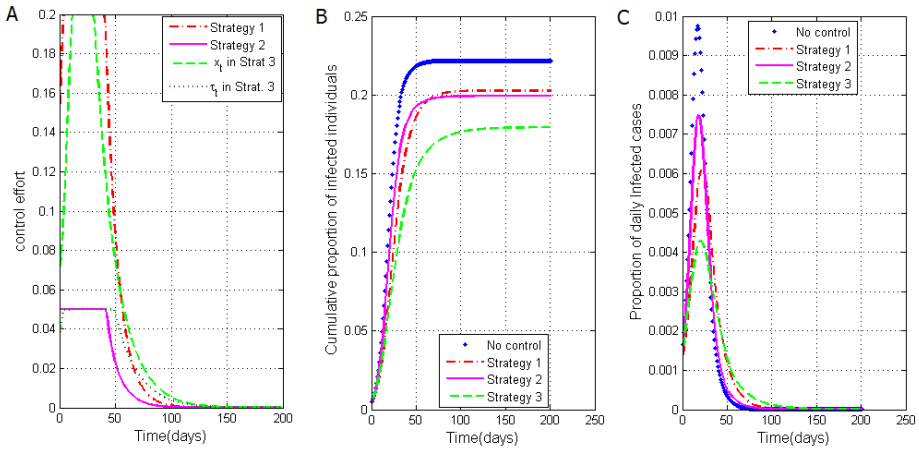

Figure 2: For $R_0 = 2.4$, the optimal solution requires the implementation of the highest permitted values for each control strategy during the first 50 days of the epidemic. Strategy 3 produces a reduction of less than 22%. Even when there is a maximum control implementation, the effort is not enough and the reduction in the final epidemic size is less significant compared to that for moderate values of R_0

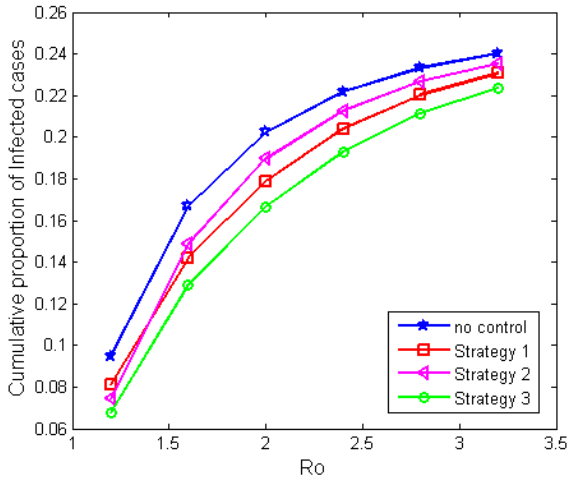

Figure 3: The comparison of final epidemic size vs. R_0 for the three Strategies is obtained by fixing the weights B_2 and B_3 of each control function. The results show that Strategy 3 yields the highest reduction of the final epidemic size.

4.2 Effects of weight constants

The role of weight constants is explored by assessing their quantitative impact in terms of the number of infected cases. The weight constants correspond to the relative costs of the effort carried out in the implementation of the algorithms leading to the identification of the optimal strategies. We study the impact of B_2 and B_3 on Strategies 1(social distancing) and 2 (antiviral treatment), respectively. We set $R_0 = 1.8$, $x_{\max} = 0.2$, and $\tau_{\max} = 0.02$. Figures 4 and 5 show the optimal control solutions computed under Strategies 1 and 2 as well as their impact on the cumulative proportion of infected individuals and daily infected cases.

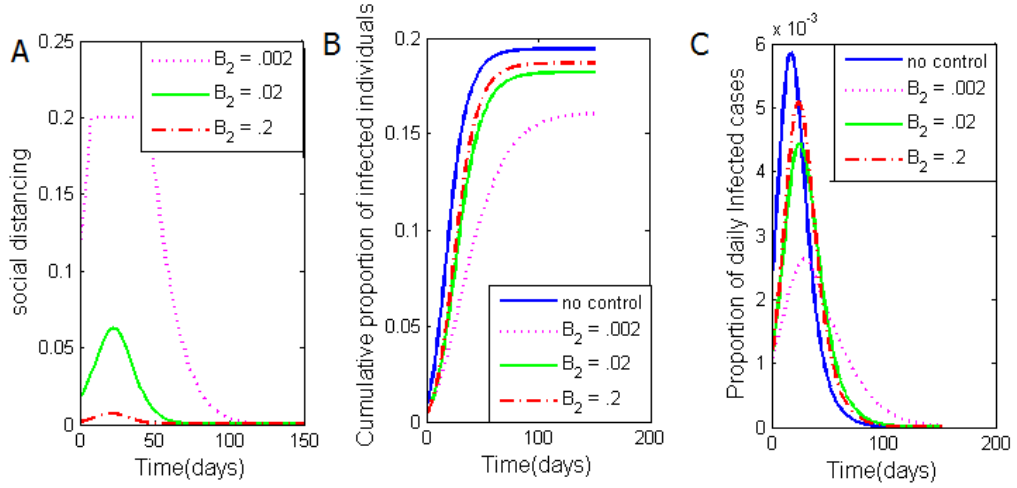

Figure 4: In Strategy 1, the value of the weight constant B_2, which correspond to the cost on social distancing is varied. For a small value of B_2, the optimal solution permits the implementation of high values of social distancing and we obtain a high reduction in the final epidemic size (20%). For a large value of B_2 we get an application of a moderate social distancing in the optimal solution then the reduction in the final epidemic size is not significant (7.5%).

The optimal control solution takes on the maximum value permitted for social distancing within the first 50 days of the epidemic when the weight constant is the smallest ($B_2 = 0.002$), Figure 4A. This high value for the social distancing control yields the highest reduction (20%) in the final epi-

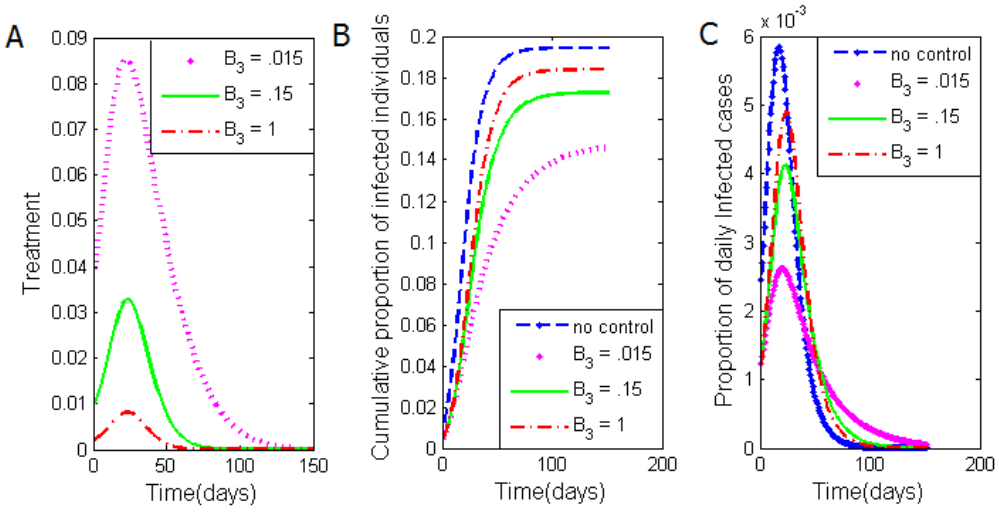

Figure 5: For strategy 2, by increasing the cost on antiviral treatment, B_3, the optimal solution permits the application of smaller value for treatment. We obtain an increase in the cumulative proportion and the proportion of daily infected cases. In contrast, when the cost is moderate the optimal solution permits the implementation of high values of treatment and we get a strong impact in the reduction of the final epidemic size (30%).

demic size (Figure 4B). However, as the weight constant (B_2) is increased to 0.2 the reduction in the final epidemic size decreases to 7.5%. Figure 4C plots the proportion of daily infected cases under each optimal control solution. Figure 4C shows the possibility of a longer delay in the peak of the epidemic as the value of the weight constant B_2 decreases.

When Strategy 2 is put in place, similar findings are observed. As the weight constant increases, reductions in the final epidemic size are observed. For example, when $B_3 = 0.015$, the reduction in the final epidemic size is almost 30% but when $B_3 = 0.15$ and $B_3 = 1$ the reductions are only 15% and 7.5%, respectively.

The cumulative proportion of infected cases without controls together with those generated under Strategies 1 and 2, respectively are plotted in Figures 6A and 6B. Figure 6A plots the results under Strategy 1 for three different values of the weight constant B_2. Small values of $B_2 = 0.002$ result in a higher reduction in the final epidemic size for all ranges of R_0. Figure 6B shows that for large values of R_0, changes in the weight constant B_3 do not

affect the solution. When $R_0 \geq 2.5$ optimal control solutions are the same for various values of B_3, a consequence of the a priori limitations placed on the controls' upper bounds.

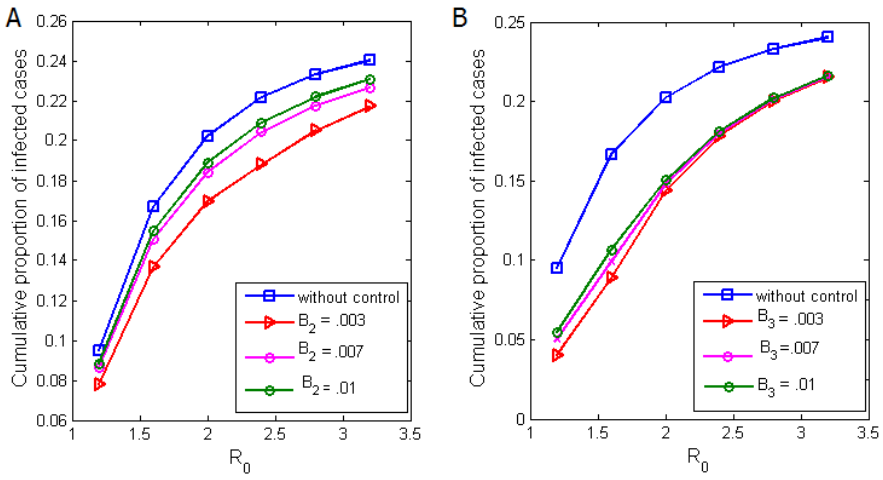

Figure 6: We plot the final epidemic size vs. R_0 for Strategies 1 and 2 by changing the weight constants for social distancing and antiviral treatment. When we have a moderate cost of social distancing, there is a reduction in the final epidemic size for every value of R_0 (A); however, by changing B_3 there is not a significant difference in the final epidemic size for $R_0 \geq 2.5$.

4.3 The effect of upper bounds on the optimal control

We study the implementation of Strategies 1 and 2 under limited resources as a results of changes in the values of the controls upper bounds: $x_{\max} \in [0.07, 0.2]$ and $\tau_{\max} \in [0.007, 0.02]$, respectively. We fix a moderate value of $R_0 = 1.8$ and set the values of the weigh constants at $B_2 = 0.004$ and $B_3 = 0.5B_2$. Figures 7A and 8A show the optimal control solution under Strategy 1 and 2, respectively. Figures 7B, C and Figures 8B, C show the effect of controls on the reduction of the final epidemic size and proportion of daily infected cases. Figure 7B shows that when the upper bound is relatively small ($x_{\max} = 0.07$), the reduction in the final epidemic size is less than 5% but when the upper bound is large ($x_{\max} = 0.20$) a reduction of 15% in the final epidemic size can be achieved.

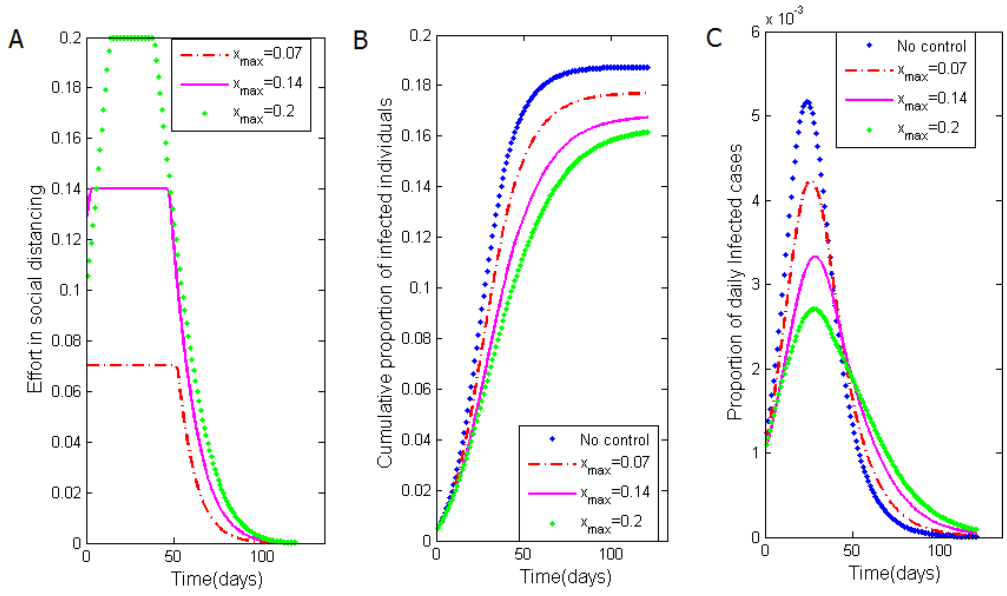

Figure 7: When the resources are limited and the upper bound is smaller ($x_{\max} = 0.07$), the reduction of the final epidemic size is small (5%). However, if the upper bound is high there is a stronger impact in the reduction of the final epidemic size, (20%).

Figure 7C shows that a reduction of 50% or more in the epidemic peak can be achieved when the upper bound increases to the maximum value $x_{\max} = 0.2$. A similar behavior is observed when the a priori upper bound in the control linked to Strategy 2 is varied. Figure 8 shows that a maximum upper bound of $\tau_{\max} = 0.02$ gives 13% reduction in the final epidemic size. In fact, when the upper bound is relatively small ($\tau_{\max} = 0.07$), the final epidemic size is reduced also but only by 5%.

5 Conclusions

A discrete model is introduced in order to study single epidemic outbreaks in the context of influenza. The use of single and dual strategies (social distancing and antiviral treatment) results in reductions in the cumulative number of infected individuals. Furthermore, we have seen that dual strategies are more efficient at reducing the final epidemic size than single policies.

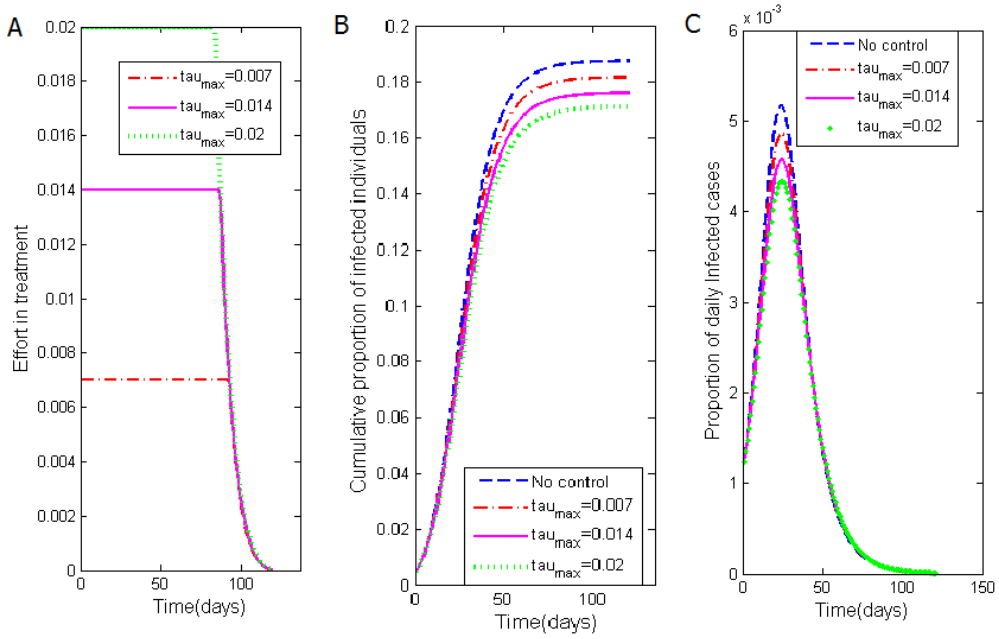

Figure 8: The impact of the control in Strategy 2 is reduced when the resources are limited. For a small upper bound, $\tau_{\max} = 0.007$, we get a small reduction of the final epidemic size (5%). When the upper bound is $\tau_{\max} = 0.02$, the final epidemic size is reduced by 13%

Our results show that under the implementation of a single policy, the social distancing strategy (Strategy 1) is more effective than the antiviral treatment strategy (Strategy 2) when $R_0 > 1.5$. Dual policies are always most effective and in this respect, our findings are consistent with those obtained recently using continuous time models [Lee et al.(2010)Lee, Chowell, and Castillo-Chavez]. In the application of every policy, we find that the intensity of the control effort is higher at the beginning of the epidemic. Furthermore, for extremely high values of R_0, $R_0 \geq 2.4$, even under the implementation of maximum effort, it is observed that the selected policies do not make a significant difference.

Recent studies show that the 2009 influenza pandemic had stronger economical impact in Mexico [Monterrubio(2010),stimson.org(2009),wisebread.com(2009)]. Unfortunately estimating the real costs associated with the selected policies (interventions measures) is difficult even in the context of the simple model

in this note. Therefore, we have focused on the use of relative costs. However, even after we have chosen the interventions strategies (policies) ranking the relative costs is often a matter of debate. In addition we did not include the impact of time delays which arise from a multitude of factors including those tied in to the development or implementation of intervention (resource-limited policies). The 2009 influenza pandemic has shown that such delays could be critically important. Fortunately, the expected negative impact of these delays never materialized due to the lack of disease severity associated with this novel influenza A-H1N1 strain.

Appendix A: Final Epidemic Size

Let $\tau_t = 0$. Then from the first equation in Model (1) we get that

$$S_{k+1} = S_0 G_0 G_1 \dots G_k$$

where

$$\ln\left(\frac{S_{k+1}}{S_0}\right) = -\frac{\beta}{N}\left(\ln G_0 + \ln G_1 + \ldots + \ln G_k\right).$$

However, since

$$\ln G_i = \ln\left(e^{-\beta\frac{I_t + mA_t}{N}}\right) = -\frac{\beta}{N}\left(I_i + mA_i\right)$$

the previous equation becomes

$$\frac{N}{\beta}\ln\left(\frac{S_0}{S_{k+1}}\right) = \sum_{i=0}^{k} I_i + m\sum_{i=0}^{k} A_i. \tag{10}$$

From the second equation in Model (1) we have that

$$A_{k+1} = qS_k(1 - G_k) + (1 - \sigma_1)\,A_k,$$

and after some rearrangement of terms, we obtain that

$$\begin{aligned} A_{k+1} - (1-\sigma_1)\,A_k &= qS_k - qS_kG_k \\ &= qS_k - qS_{k+1}. \end{aligned}$$

Summing over k we get that

$$\sigma_1 \sum_{k=0}^{n} A_k - A_0 = q\left(S_0 - S_n\right).$$

But $A_0 = 0$ and $S_0 \approx N$, and therefore

$$\sum_{k=0}^{n} A_k = \frac{q}{\sigma_1} (N - S_n). \tag{11}$$

By adding equation S, A and I in Model (1) we obtain

$$S_{k+1} + A_{k+1} + I_{k+1} = S_k + (1 - \sigma_1) A_k + (1 - \sigma_1)(1 - \delta) I_k.$$

Rearrange the terms of the above equation to get

$$(S_{k+1} - S_k) + (A_{k+1} - (1 - \sigma_1) A_k) + (I_{k+1} - (1 - \sigma_1)(1 - \delta) I_k) = 0,$$

and summing over k we get that

$$S_n - S_0 + \sigma_1 \sum_{k=0}^{n} A_k - A_0 + (1 - (1 - \sigma_1)(1 - \delta)) \sum_{k=0}^{n} I_k - I_0 = 0,$$

hence

$$\sum_{k=0}^{n} I_k = \frac{1}{1 - (1 - \sigma_1)(1 - \delta)} \left[N - S_n - \sigma_1 \sum_{k=0}^{n} A_k \right]. \tag{12}$$

Substituting (11) into (12) yields

$$\sum_{k=0}^{n} I_k = \frac{1}{1 - (1 - \sigma_1)(1 - \delta)} \left[N - S_n - q (N - S_n) \right].$$

Therefore,

$$\sum_{k=0}^{n} I_k = \frac{1}{1 - (1 - \sigma_1)(1 - \delta)} \left[(1 - q)(N - S_n) \right]. \tag{13}$$

Substituting (11) and (13) into (10) gives

$$\frac{N}{\beta} \ln \left(\frac{S_0}{S_{n+1}} \right) = \left[\frac{1}{1 - (1 - \sigma_1)(1 - \delta)} (1 - q) + m \frac{q}{\sigma_1} \right] (N - S_n).$$

Taking the limit as $n \to \infty$ leads to the final size relation,

$$\ln \left(\frac{S_0}{S_\infty} \right) = \beta \left[\frac{1}{1 - (1 - \sigma_1)(1 - \delta)} (1 - q) + m \frac{q}{\sigma_1} \right] \left(1 - \frac{S_\infty}{N} \right),$$

which can be written as

$$\ln\left(\frac{S_0}{S_\infty}\right) = R_0\left(1-\frac{S_\infty}{N}\right).$$

Thus, the basic reproductive number is given by

$$R_0 = \beta\left(\frac{(1-q)}{1-(1-\sigma_1)(1-\delta)} + m\frac{q}{\sigma_1}\right).$$

Appendix B: Proof of Result 2.1

Let

$$f(x) = \ln\left(\frac{S_0}{x}\right) - R_0\left(1-\frac{x}{N}\right) \quad \text{for} \quad 0 < x \leq N. \tag{14}$$

The result can be verified easily for $R_0 < 1$. Let us consider $R_0 > 1$; f is a decreasing function for $x < \frac{N}{R_0}$ and $\frac{N}{R_0}$ is the unique critical point of f . Since $f(N) = 0$ then $S_\infty < \frac{N}{R_0} < N$ and $f'(S_\infty) < 0$. Hence, $f < 0$ if and only if $S_\infty < x < N$. By hypothesis $f(S_\infty^{wc}) < 0$, then $S_\infty < S_\infty^{wc}$.

Appendix C

We focus on Strategy 3, that is, when antiviral treatment and social distancing are implemented. The problem formulation is given in expressions (6) and (7) from where we define the Hamiltonian,

$$\begin{aligned} H = {} & \frac{1}{2}\left(B_0 I_t^2 + B_2 x_t^2 + B_3 \tau_t^2 + B_4 D_t^2\right) + \lambda_{t+1}^1 S_t G_t \\ & + \lambda_{t+1}^2 (q S_t (1-G_t) + (1-\sigma_0) A_t) \\ & + \lambda_{t+1}^3 ((1-q) S_t (1-G_t) + (1-\tau)(1-\sigma_1)(1-\delta) I_t) \\ & + \lambda_{t+1}^4 ((1-\sigma_2) T_t + \tau (1-\sigma_1)(1-\delta) I_t) \\ & + \lambda_{t+1}^5 (R_t + \sigma_0 A_t + \sigma_1 (1-\delta) I_t + \sigma_2 T_t) + \lambda_{t+1}^6 (D_t + \delta I_t), \end{aligned} \tag{15}$$

where $G_t = \exp\left(-\beta(1-x_t)\frac{I_t+mA_t+\rho T_t}{N}\right)$. The adjoint equations associated with the problem are

$$\begin{aligned}
\lambda_t^1 &= G_t\lambda_{t+1}^1 + \left((q\lambda_{t+1}^2 + (1-q)\lambda_{t+1}^3)\right)(1-G_t) \\
\lambda_t^2 &= S_tG_t\tfrac{\beta m}{N}(1-x_t)L_{t+1} + (1-\sigma_1)\lambda_{t+1}^2 + \sigma_1\lambda_{t+1}^5 \\
\lambda_t^3 &= B_0I_t + S_tG_t\tfrac{\beta}{N}(1-x_t)L_{t+1} + \\
&\quad (1-\delta)\left[(1-\sigma_1)\left((1-\tau)\lambda_{t+1}^3 + \tau\lambda_{t+1}^4\right) + \sigma_1\lambda_{t+1}^5\right] + \delta\lambda_{t+1}^6 \\
\lambda_t^4 &= S_tG_t\tfrac{\beta\rho}{N}(1-x_t)L_{t+1} + (1-\sigma_2)\lambda_{t+1}^4 + \sigma_2\lambda_{t+1}^5 \\
\lambda_t^5 &= \lambda_{t+1}^5 \\
\lambda_t^6 &= B_1D_t + \lambda_{t+1}^6,
\end{aligned} \tag{16}$$

for $L_{t+1} = -\lambda_{t+1}^1 + q\lambda_{t+1}^2 + (1-q)\lambda_{t+1}^3$. With transversality conditions

$$\lambda^i(T_f) = 0, \quad \text{for} \quad i = 1, 2, ...6$$

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