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Control of Epidemics by Vaccination

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Abstract— **This paper investigates the problem of controlling epidemics through different vaccination strategies. A simple, constant vaccination rate is considered initially, followed by a more elaborate model, incorporating realistic delay effects. Recent results on optimal impulsive control for delay systems are used to determine a pulse vaccination strategy for controlling the epidemic spread of a disease. It is shown that the optimal strategy is not necessarily periodic.**

I. Introduction

The health and socioeconomic risks posed by severe and sudden epidemics of infectious diseases like SARS, Avian Flu or West Nile Virus, or the assessed impact of a potential influenza pandemic, measles pre and post-eradication outbreaks or bio-terrorist attacks, are compelling modern societies to design and implement more effective control and preparedness programs. The work in this paper contributes to a growing literature on applying optimal control techniques to epidemiology, e.g. [5], [7]. The ultimate intention of such studies is to provide a body of evidence that decision makers and institutions can use in designing policy recommendations and interventions.

The first model of an epidemic was suggested by Bernoulli in 1760. He used this model to explain the basic control effects obtained through population immunization, and the advantages of vaccination in order to prevent an epidemic. Simple mathematical models to study the transmission dynamics belong to the class of compartment models, and are governed by mass-action laws [6], [8]. The rate of spread of infection is hereby assumed to be proportional to the density of susceptible people and the density of infected people (strong homogenous mixing). Simpler models, based on 'weak homogenous mixing' (rate of new infections proportional to the number of susceptibles) are explored in [2]. One parameter stands out in these models: the ratio of the rate of infection to the rate of recovery, denoted by r_0, called the basic reproduction number. It is the average number of new cases produced when one infective is introduced into a completely susceptible host population. A basic result in modern epidemiology is the existence of a threshold value for the reproduction number. If r_0 is below the threshold, an epidemic outbreak does not follow the introduction of a few infectious individuals in the community. For example measles has a r_0 on the order of 12-15 [1].

The biological processes of sudden and severe epidemics are inherently nonlinear, and exhibit fundamentally different dynamic behaviors from linear systems (e.g. multiple equilibria, limit cycles, and chaos). In addition, more complex nonlinear models encompassing spatial variation (i.e. mixing locally within households and globally throughout the population, temporal variation (age structure) and delays [12] are also required to give added realism, which makes the control problem even harder. Hence, regarding the control of epidemics, few analytical results exist. A notable and recent exception is the work of [5]. Nonetheless, analytical or numerical approximations for infection control measures such as vaccination, dose profile and timing in pulse vaccination regimes [11], isolation and quarantine, screening or other public health interventions are vital for controlling severe epidemics.

When using finite dimensional models, it is clear that when the initial state is reached again through the action of the control, the process will be periodic [4]. This is the principle behind pulse vaccination [9], although true periodicity of the state is not assumed. However, when delays are present the system is inherently infinite dimensional, and it is unlikely that the same state may be reached twice. Hence the premise that a periodic pulse vaccination strategy is optimal is false. Techniques recently developed by the authors [13] for optimal impulsive control for systems with delays will be applied in order to overcome this problem.

In this paper, we address the control problem from two different points-of-view. First we investigate and evaluate a control strategy associated with a constant immunization rate, in Section II. In Section III, we recall the necessary conditions and algorithm for optimal impulsive control in the presence of a delay, followed by a study of optimal pulse-vaccinations, in Section IV.

II. Disease and Immunization Models

In this section we discuss the main models for epidemic outbreaks in order to obtain a formulation amenable to control. In particular, we will discuss different vaccination strategies, and we start by considering the simplified, so-called SIS-model, in order to gain some initial insight [6]. Let S be the fraction of the population that is susceptible to the disease, and let I be the fraction corresponding to the infected individuals. In that case, the dynamical equations

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governing the epidemics are

$$\dot{S} = -\beta SI + \rho I \quad (1)$$
$$\dot{I} = \beta SI - \rho I. \quad (2)$$

The interpretation here is that β is the rate of infection, while ρ corresponds to the recovery rate. It should be noted directly that $S+I=1$, and hence we can reduce this model to the first order nonlinear model

$$\dot{I} = \beta I(1-I) - \rho I. \quad (3)$$

There are two equilibria to this equation, namely $I=0$ (the disease-free state) and $I=(\beta-\rho)/\beta$ (the endemic equilibrium). Moreover, the solution to this differential equation is, for $I_0 \neq 0$ and $\beta \neq \rho$

$$I(t) = \frac{\mathrm{e}^{(\beta-\rho)\mathrm{t}}}{\frac{1}{I_0} + \frac{\beta}{\beta-\rho}\mathrm{e}^{(\beta-\rho)\mathrm{t}}}, \quad (4)$$

while $I(t) \equiv 0$ if $I_0 = 0$.

Now, if $\beta - \rho > 0$, then we can define $r_0 = \beta/\rho$ to be the reproductive rate (or reproduction number) of the epidemic, with the state converging to the endemic equilibrium $I(\infty) = 1 - r_0^{-1}$.

A. Constant Immunization Rates

In order to apply control to this problem, we need to carefully model the different ways in which epidemics can be managed, and we start by considering the vaccination of the population at a fixed rate α. It is assumed that the injection of dead or live but attenuated disease microorganisms into members of the population results in the generation of antibodies in the vaccinated individuals. If a proportion α of the susceptibles is vaccinated successfully, then these individuals are assumed to become immune and are removed from the original S class. In other words, let R be the fraction of the population of individuals that are removed through immunization, which results in a so-called SIR-model. The limited time effectiveness of the vaccine is modelled by a return rate γ, of the immunized to the susceptible class. Hence, we now have

$$\dot{S} = -\beta SI + \rho I - \alpha S + \gamma R \quad (5)$$
$$\dot{I} = \beta SI - \rho I \quad (6)$$
$$\dot{R} = \alpha S - \gamma R. \quad (7)$$

Here $R+I+S=1$, and we thus get the second order model

$$\dot{I} = \beta I(1-I-R) - \rho I \quad (8)$$
$$\dot{R} = \alpha(1-I-R) - \gamma R. \quad (9)$$

A disease-free equilibrium $I=0$, $R=\alpha/(\alpha+\gamma)$ exists, as well as an endemic equilibrium $I = 1-(1+r)/r_0$, $R = r/r_0$, provided that $r = \alpha/\gamma < r_0 - 1$, which is the fraction of (temporary) immune individuals. For $r_0 > 1$, the linearized model about the endemic equilibrium is

$$\dot{\tilde{I}} = -\beta I_e \tilde{I} - \beta I_e \tilde{R} \quad (10)$$
$$\dot{\tilde{R}} = -\alpha \tilde{I} - (\alpha+\gamma)\tilde{R}. \quad (11)$$

Unless both $r_0 - r - 1$ and $r_0 + (1+r)(\gamma/\rho - 1)$ are positive, this equilibrium is unstable.

Likewise, the linearized model about the disease free equilibrium is

$$\dot{\tilde{I}} = \left[\frac{\beta\gamma}{\alpha+\gamma} - \rho\right]\tilde{I} \quad (12)$$
$$\dot{\tilde{R}} = -\alpha \tilde{I} - (\alpha+\gamma)\tilde{R}. \quad (13)$$

This equilibrium is stable for a constant rate α if $r_0 - r - 1 < 0$, in which case the endemic equilibrium is repelling.

Hence for $r_0 < 1$ no vaccination is required in order to maintain a disease-free population, while for $r_0 > 1$, the disease free state is robustly maintained for a sufficiently large vaccination rate $\alpha > \alpha_0$, given the threshold value

$$\alpha_0 = \gamma\,(r_0 - 1)\,. \quad (14)$$

What is the cost associated with this disease free equilibrium? If no disease is present ($I = 0$), in principle $\alpha = 0$ may be taken, and therefore no costs (neither vaccination nor care for the sick) will be incurred. However this situation is not robust if $r_0 > 1$, as seen above. Moreover, the idea of using a constant vaccination rate is not very realistic. In practice, population groups are vaccinated during very short time intervals for logistic reasons. This means that impulse control is a better control model than the constant vaccination rate model.

B. Pulse Vaccinations

A different policy, not captured with the previous model, is a policy where an entire block of the susceptible population is vaccinated at once, and thus removed. As such, the vaccination campaign is "instantaneous", with respect to the time scales of the disease, and it is modelled as an impulsive effect. Dynamics and control of such 'impulsive systems' are described in [4]. Moreover, in order to get a realistic model, we will assume that people do not instantaneously become healthy and/or immune. Instead, this is a delayed phenomenon that must be modelled using time delays. Thus, for the remainder of this paper, we will consider the autonomous model

$$\dot{S}(t) = -\beta S(t)I(t) + \rho I(t-\tau) \quad (15)$$
$$\dot{I}(t) = \beta S(t)I(t) - (\rho+\kappa)I(t-\tau) \quad (16)$$
$$\dot{R}(t) = \kappa I(t-\tau), \quad (17)$$

for describing the dynamics between the pulse vaccination campaigns. Note here that $\tau > 0$ denotes the delay-time, κ corresponds to the rate at which infected individuals become immune, and ρ is the rate at which they become healthy yet not immune. Moreover, we have assumed that $\gamma = 0$, i.e.

individuals do not become susceptible to the disease once they have been immunized, which is reasonable for most short-to-medium time-scale models of epidemics. (e.g., Flu vaccination is typically an efficient protection during one season.)

Now, this model needs to be augmented by the impulsive vaccination effects. Assume that these vaccinations take place at times T_k, $k = 1, 2, \ldots$, at which times a fraction of the healthy individuals are moved from the S class to the R class. In other words,

$$\begin{aligned} S(T_k^+) &= S(T_k^-) - v_k && (18)\\ I(T_k^+) &= I(T_k^-) && (19)\\ R(T_k^+) &= R(\tau_k^-) + v_k. && (20) \end{aligned}$$

The delayed, optimal impulsive control problem thus have to be solved both for the magnitudes v_k and for the vaccination instants T_k, $k = 1, 2, \ldots$, which will be the main focus of the next section.

III. Optimal Impulse Control for Point Delay Systems

A. Optimality Conditions

In order to be able to solve the optimal immunization problem, some results on optimal impulse control must be recalled. These results were recently developed by the authors in [13], and for sake of easy reference, we restate them here. To fix ideas, let the autonomous system under consideration be modelled by

$$\dot{x} = f(x) + g(x_\tau), \tag{21}$$

where $x_\tau = x(t - \tau)$, and where $x(\theta)$ is given for $-\tau < \theta < 0$. Moreover, let the effect of the impulsive inputs be given by

$$x(T_i^+) = x(T_i^-) + G(x(T_i^-), u_i, T_i). \tag{22}$$

The amplitudes, u_i, and instants, T_i, are to be chosen such that a performance index

$$J = \int_0^{t_f} L(x(t))dt + \sum_{i=1}^{N-1} K(x(T_i^-), u_i, T_i) \tag{23}$$

is optimized.

We will assume that the vector fields $f(x)$ and $g(x)$ as well as the function $L(x)$ are smooth, and we let $N-1$ be the total number of impulses, with $T_0 = 0$ and $T_N = t_f$ being fixed. In [13], the following theorem was proved:

Theorem 3.1: The impulsive system in Equations 21 and 22 minimizes the performance index J if the magnitudes u_i and times T_i are chosen as follows:

Define:

$$\begin{aligned} H_i &= L(x) + \lambda_i^T(f(x) + g(x_\tau)) && (24)\\ M_i &= K(x(T_i^-), u_i, T_i) + \mu_i G(x(T_i^-), u_i, T_i). && (25) \end{aligned}$$

Euler-Lagrange Equations:

$$\dot{\lambda}_i = -\left(\frac{\partial L}{\partial x}\right)^T - \left(\frac{\partial f}{\partial x}\right)^T \lambda_i - \chi_i^+ \left(\frac{\partial g}{\partial x}\right)^T \lambda_i^\tau - \chi_{i+1}^- \left(\frac{\partial g}{\partial x}\right)^T \lambda_{i+1}^\tau, \tag{26}$$

with $T_{i-1} < t < T_i,\ i = 1, \ldots, N-1$, and where $\chi_i^+(t) = 1$ if $t \in [T_{i-1}, T_i - \tau]$ and 0 otherwise, $\chi_{i+1}^-(t) = 1$ if $t \in [T_i - \tau, T_i]$ and 0 otherwise, and $\lambda_i^\tau = \lambda_i(t + \tau)$. Moreover,

$$\dot{\lambda}_N = -\left(\frac{\partial L}{\partial x}\right)^T - \left(\frac{\partial f}{\partial x}\right)^T \lambda_N - \chi_N^+ \left(\frac{\partial g}{\partial x}\right)^T \lambda_N^\tau. \tag{27}$$

Boundary Conditions:

$$\begin{aligned} \lambda_N(T_N) &= 0 && (28)\\ \lambda_i(T_i^-) &= \lambda_{i+1}(T_i^+) + \left(\frac{\partial M_i}{\partial x}\right)^T. && (29) \end{aligned}$$

Multipliers:

$$\begin{aligned} \mu_i &= \lambda_{i+1}(T_i^+),\ i = 1, \ldots, N-1 && (30)\\ \mu_N &= -\left(\frac{\partial M_N}{\partial x}\right)^T. && (31) \end{aligned}$$

Optimality Conditions:

$$\begin{aligned} &\frac{dJ}{du_i} = \frac{\partial M_i}{\partial u_i} = 0 && (32)\\ &\frac{dJ}{dT_i} = H_i(T_i^-) - H_{i+1}(T_i^+) + \frac{\partial M_i}{\partial T_i} && (33)\\ &\qquad + \lambda_{i+1}(T_i + \tau)^T (g(x(T_i^+)) - g(x(T_i^-))) = 0. \end{aligned}$$

These conditions may seem quite involved, but as we will see in the next section, when applied to the impulse vaccination problem, they reduce down to a nice and numerically easy-to-handle set of equations.

B. Gradient Descent

The reason why the formulas derived above are particularly easy to work with is that they give us access to a very straight-forward numerical algorithm.

For each iteration k, let $\theta(k) = (T_1(k), u_1(k), ..., T_{N-1}(k), u_{N-1}(k))^T$ be the vector of control variables, and compute the following:

1) Compute $x(t)$ forward in time on $[t_0, t_f]$ by integrating Equations 21 and 22 from $x(t_0) = x_0$.
2) Compute $\lambda(t)$ backward in time from t_f to t_0 by integrating Equations 26-29.
3) Use Equations 32 and 33 to compute $\nabla_\theta J = (\frac{dJ}{dT_1}, \frac{dJ}{du_1}, \ldots, \frac{dJ}{dT_{N-1}}, \frac{dJ}{du_{N-1}})$.
4) Update θ as follow :
$$\theta(k+1) = \theta(k) - l(k)\nabla_\theta J^T,$$
where $l(k)$ is the stepsize, e.g. given by the Armijo algorithm [3].
5) Repeat.

Note that the cost function J may be non-convex which means that we can only expect the method to reach a local minimum. But, as we will see, it still can give quite significant reductions in cost.

IV. Optimum Pulse Vaccination

A. Delayed SIR-model

Although an 'impulse' control, we keep the term 'pulse vaccination' as it is established throughout the epidemiology literature. Let $x = (S, I)^T$ and consider, as before, the delayed model in Equations 15-20

$$\begin{aligned} \dot{S} &= -\beta SI + \rho I(t-\tau) && (34)\\ \dot{I} &= \beta SI - (\rho+\kappa) I(t-\tau) && (35)\\ S(T^+) &= S(T^-) - v,\ v \in [0, S(T^-)] && (36)\\ I(T^+) &= I(T^-). && (37) \end{aligned}$$

Here we have assumed that only one vaccination takes place, and we note that, according to the notation in the previous section,

$$\begin{aligned} f(x) &= \begin{pmatrix} -\beta SI \\ \beta SI \end{pmatrix}, & \frac{\partial f}{\partial x} &= \begin{pmatrix} -\beta I & -\beta S \\ \beta I & \beta S \end{pmatrix}\\ g(x) &= \begin{pmatrix} \rho I \\ -(\rho+\kappa) I \end{pmatrix}, & \frac{\partial g}{\partial x} &= \begin{pmatrix} 0 & \rho \\ 0 & -(\rho+\kappa) \end{pmatrix}\\ G(x(T^-), v, T) &= \begin{pmatrix} -v \\ 0 \end{pmatrix} \end{aligned} \tag{38}$$

Moreover, we assume that the cost to be minimized is

$$J(v, T) = cv^2 + \int_0^{t_f} I(t)dt. \tag{39}$$

The integral term measures the burden of disease (total time spent sick in the population) during the epidemic, and the quadratic control cost reflects the added logistical burden when large populations need to be vaccinated. Note that a purely linear vaccination cost, without imposing the constraint $v \geq 0$, may lead to inadmissible controls [10]. Hence, in this problem:

$$\begin{aligned} &L(x) = I && \frac{\partial L}{\partial x} = (0, 1)\\ &K(x(T^-), v, T) = cv^2 \end{aligned} \tag{40}$$

Moreover, $M = K + \mu^T G$ in Theorem 3.1 satisfies $\partial M/\partial x = 0$, which implies that $\lambda_1(T^-) = \lambda_2(T^+)$, i.e., the costate is continuous. We let λ denote this single, continuous costate and note that we only need to solve for λ on the time interval $[T, t_f]$, with $\lambda(t_f) = 0$. After solving for λ, we get that $\mu = \lambda(T)$, and hence that the first optimality condition implies

$$\frac{dJ}{dv} = 2cv + \lambda(T)^T \begin{pmatrix} -1 \\ 0 \end{pmatrix} = 0. \tag{41}$$

In order to arrive at the second optimality condition, we note that $g(x(T^+)) = g(x(T^-))$ since g only depends on I, which does not experience an impulse at time T. Moreover, it is straightforward to show that

$$H(T^-) - H(T^+) = \lambda(T)^T (f(x(T^-)) - f(x(T^+))), \tag{42}$$

where

$$f(x(T^-)) - f(x(T^+)) = \begin{pmatrix} -\beta v I(T) \\ \beta v I(T) \end{pmatrix}. \tag{43}$$

This, combined with the fact that $\partial M/\partial T = 0$, gives

$$\frac{dJ}{dT} = \beta v I(T) \lambda(T)^T \begin{pmatrix} -1 \\ 1 \end{pmatrix} = 0. \tag{44}$$

B. Numerical Example

We consider the situation with one impulse with parameters

$$\begin{aligned} &\beta = 0.8,\ \rho = 0.1,\ \kappa = 0.5\\ &t_0 = 0,\ t_f = 5,\ \tau = 0.5\\ &c = 3, \end{aligned}$$

which corresponds to an epidemic slightly less contagious than measles.

A constant stepsize $l = 0.1$ is taken. The results are shown in Figures 1-3, from which it can be seen that after 24 iterations, a local optimum is obtained, with

$$T \approx 0.34,\ v \approx 0.1.$$

This gives a minimal cost $J \approx 0.517$.

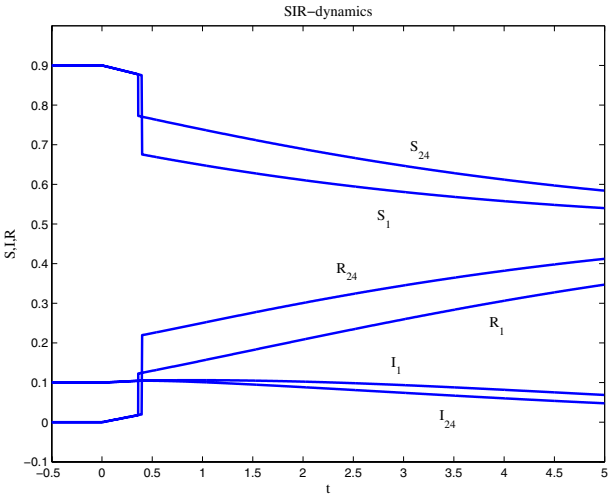

Fig. 1. SIR dynamics (1 impulse)

If we want to study the case where with multiple impulses, it is straight-forward to show that, given the disease dynamics in Equations 15-20, augmented to allow for multiple impulses, and with the new cost being

$$J(v_1, \ldots, v_{N-1}, T_1, \ldots, T_{N-1}) = \sum_{i=1}^{N-1} cv_i^2 + \int_{t_0}^{t_f} I(t)dt, \tag{45}$$

the optimlity conditions remain the same. In fact, we get that λ is still continuous on $[t_0, t_f]$ as well as

$$\begin{aligned} \frac{dJ}{dv_i} &= 2cv_i + \lambda(T_i)^T \begin{pmatrix} -1 \\ 0 \end{pmatrix} && (46)\\ \frac{dJ}{dT_i} &= \beta v_i I(T_i) \lambda(T_i)^T \begin{pmatrix} -1 \\ 1 \end{pmatrix}, && (47) \end{aligned}$$

for $i = 1, \ldots, N-1$.

An example with three impulses is shown in Figures 4-5, with the same choice of parameters as in the one-impulse case previously discussed.

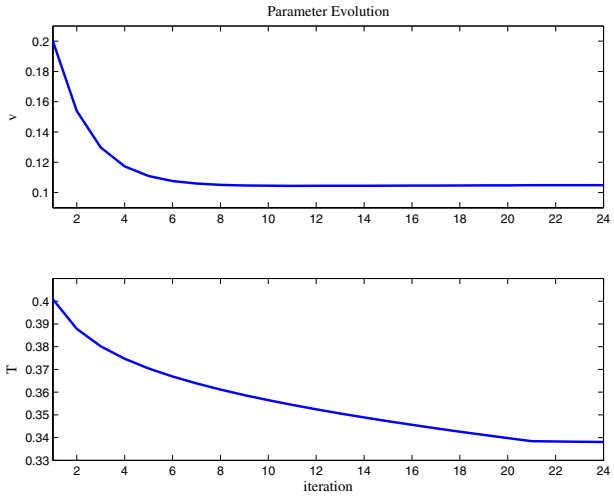

Fig. 2. Parameter Evolution (1 impulse)

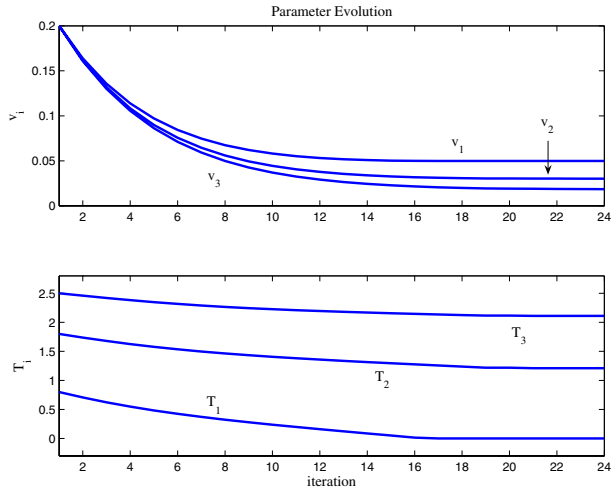

Fig. 4. Parameter Evolution (3 impusles)

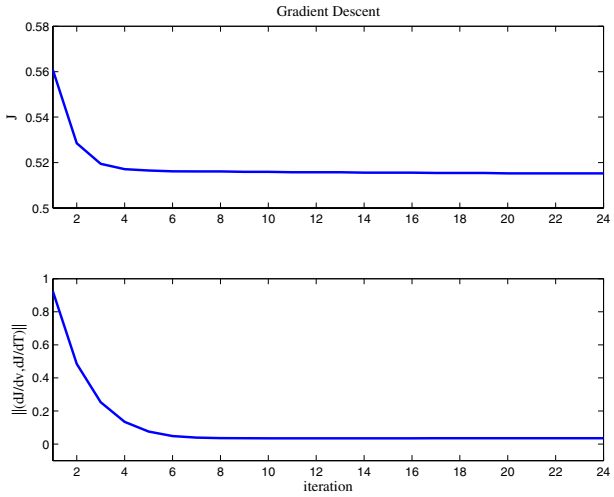

Fig. 3. Gradient Descent (1 impulse)

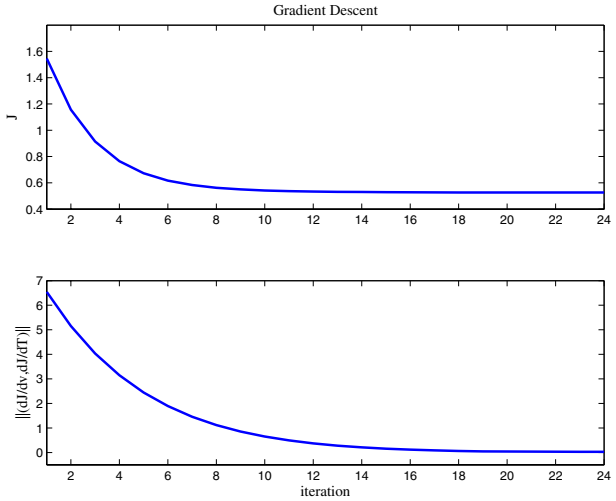

Fig. 5. Gradient Descent (3 impulses)

V. Conclusions

We have used recently developed results on optimal impulsive control for time delay systems in the problem of control of an epidemic through pulse vaccination. For added realism, delays are explicitly incorporated in the epidemiological model. It was shown that the conditions for optimality are easily amenable by an iterative gradient type numerical algorithm. Future work will include multi-pulse strategies. We expect that current policies of *periodic* vaccination pulses [9], [11] can be improved upon. This will then provide a 'proof of principle' with which more realistic models for disease may be attacked.

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