Controlling the Eradication of Polio

Ryan Hernandez

May 1, 2003

1 Introduction

Poliomyelitis is characterized by fever, motor paralysis, and atrophy of skeletal muscles (acute flaccid paralysis, AFP). The crippling virus has disabled nearly 20 million people living today [11]. Soon, however, this virus will no longer hurt our children. Since its creation in 1988, the Global Polio Eradication Initiative has helped cut the global toll of polio paralysis from an estimated 350,000 to fewer than 500 in 2001 [11]. After being deemed eradicated, polio will become the second virus to have been eradicated from the world (the first being smallpox in 1980 [10]). The goal of polio eradication has been met in most parts of the world (WHO deemed the Americas Polio-free in 1994 [11] and the 51 countries representing the EURO region were certified polio-free in June 2002 [1]), and each country that has citizens suffering from the disease has been given a plan of action for eradication [1].

There are two main vaccines that are used to build the human immune system: oral poliovirus vaccine and inactivated poliovirus vaccine. OPV, as its name suggests can be administered orally, either as a drop into the mouth, or on a sugar pill. The benefits of this vaccine are that it does not require a trained medical staff for the immunization of people, nor does it require sterile injection equipment. The main cost of using this vaccination is that it is a strain of "live" virus, hence those given this vaccine enter an infectious stage, and there is a risk of suffering the consequences of contracting polio when using it. IPV is a "dead" form of the virus, hence there is no risk of contracting polio from the vaccine, however, it is not completely effective. Only a fraction of those who receive this vaccine become completely immune, whereas others enter a stage of reduced susceptibility (hence can still contract the wild-strain of poliovirus). This vaccine can only be administered through an injection. This creates the need for trained medical staff and the use of large amounts of sterile injection equipment (which is by no means inexpensive) [11].

The main method by which developing countries vaccinate the population is by organizing national immunization days (NIDs). These days are organized by many groups international organizations (one could see the schedule of national immunization days for each country by visiting <http://www.unicef.org/polio/nidsched.htm>). Generally, these programs target a specific age group (mostly children), and one could be vaccinated multiple times.

The goal of mathematically modeling polio is to predict the transmission of polio. Models including vaccination dynamics generally seek to find some minimum vaccination level such that the virus will be eradicated. The goal here is to determine an optimal polio eradication strategy for a given country by subjecting a system of differential equation to the theory of optimal control.

2 Mathematical Models of Poliomyelitis

One of the more recent deterministic models of polio transmission and vaccination provides a system of differential equations for each vaccine separately [4]. Various other models have addressed various aspects of the transmission of poliovirus. For example, Cvjetanovic, et. al. considered an age structured model [2]. This would be key for looking at the effects of a national immunization day where only those from a certain age bracket are being vaccinated.

2.1 The OPV Model

The OPV model of Eichner and Hadeler [4] considers 4 sub-populations: the fraction of the population currently susceptible (s); the fraction of the population that has been vaccinated, but are still in the infective stage (v); the fraction of the population that has been infected by wild poliovirus (w); and the fraction of the population that has become immune (r). In this model, the authors assume a constant population, and hence the birth rate = death rate = μ. The model is as follows:

$$\dot{s} = (1-p)\mu - \beta_w sw - \beta_v sv - \mu s \quad (1)$$

$$\dot{v} = p\mu + \beta_v sv - \gamma_v v - \mu v \quad (2)$$

$$\dot{w} = \beta_w sw - \gamma_w w - \mu w \quad (3)$$

$$\dot{r} = \gamma_w w + \gamma_v v - \mu r \quad (4)$$

where p is the constant fraction of new births that are vaccinated (the authors assume vaccination at birth), μ is both the birth and death rate of the population, β_v and β_w are the infection rates that someone in population v and w (resp.) contacts and infects a susceptible individual, and γ_v and γ_w are the recovery rates of population v and w (resp.). It is of interest to note that since we have a constant population we have the following relationship: $s + v + w + r = 1$, hence we need only consider the 3 dimensional system of (s, v, w).

Following the analysis of Eichner and Hadeler on this model, we can find the basic reproductive numbers, R_v and R_w, of the v and w populations (resp.). The basic reproductive number determines the number of people that will be infected by an average infected person. If $R_w \geq 1$, the virus is endemic. In this case we have

$$R_v = \frac{\beta_v}{\gamma_v + \mu} \tag{5}$$

$$R_w = \frac{\beta_w}{\gamma_w + \mu}. \tag{6}$$

In general, R_w and R_v are greater than one, thus the disease is endemic and hence it is required that we use vaccinations to force the system into a virus-free equilibrium (or uninfected). The uninfected equilibrium can by found by setting $w = 0$ and solving for $\bar{s}$ and $\bar{v}$ by setting $\dot{s} = 0$ and $\dot{v} = 0$. From this we find

$$\bar{s} = \frac{R_v + 1}{2R_v} - \frac{1}{2R_v}\{(R_v - 1)^2 + 4pR_v\}^{1/2} \tag{7}$$

$$\bar{v} = \frac{\mu(1 - \bar{s})}{\mu + \gamma_v}. \tag{8}$$

However, since we assume that we are not yet on an uninfected equilibrium trajectory, we solve the (s,v,w) system for equilibrium and find

$$\hat{s} = \frac{1}{R_w} \tag{9}$$

$$\hat{v} = \frac{p\mu}{\beta_v} \cdot \frac{R_w R_v}{R_w - R_v} \tag{10}$$

$$\hat{w} = \frac{\mu}{\beta_w}\left(R_w - 1 - \frac{pR_w^2}{R_w - R_v}\right). \tag{11}$$

Noticing that both $\hat{v}$ and $\hat{w}$ are functions of p, we can set $\hat{w} = 0$ and solve for the critical value $p = p^*$ that would force $w(t) \to 0$. We find

$$p^* = \left(1 - \frac{1}{R_w}\right)\left(1 - \frac{R_v}{R_w}\right), \tag{12}$$

hence for all $p > p^*$ the uninfected equilibrium becomes locally stable (proved in [4]).

2.1.1 OPV Simulations

Eichner and Hadeler did not include any numerical simulations with this model, but did provide parameter values for an arbitrary developing country (see table at end of section for parameter values used). Taking these parameter values, we can use Matlab's ode solvers to simulate their results. By testing the system with both the stiff and non-stiff solvers (ode15s and ode45, resp., with an absolute and relative error tolerance $1e-10$), we find that the non-stiff solver is more efficient, and hence conclude that this is a non-stiff system.

By substituting the values of the parameters into the basic reproductive numbers (R_v and R_w) and critical vaccination level (p^*), we see that

$$\begin{aligned} R_v &= 2.99 \\ R_w &= 11.98 \\ p^* &= 0.6877. \end{aligned}$$

The general dynamics of the system in the absence of vaccination ($p = 0$) can be seen in figure 1. An interesting question is of the dynamics of this system when insufficient vaccination

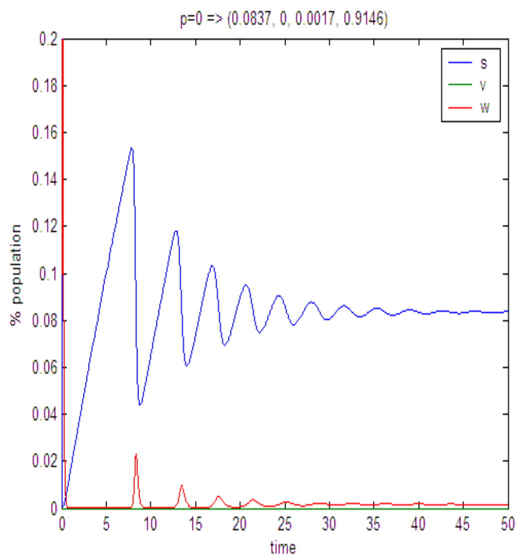

Figure 1: OPV model in the absence of vaccination.

is taking place. The dynamic of the model when $p = 0.1$ can be viewed in figure 2. When we set $p = p^*$, we see that $w \to 0$ (see figure 3), however this happens relatively quickly, and leads one to question the quantitative results of this system. w only reaches zero in the limit, however since we are dealing with a finite population, when w is sufficiently small, it will represent a population size of less than one person, thus the infected population would be effectively zero.

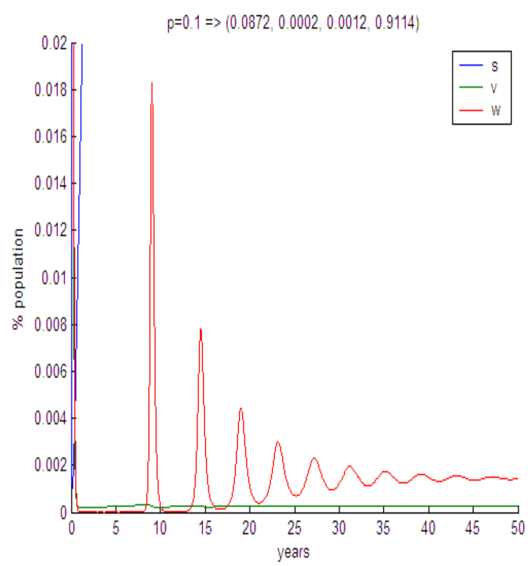

Figure 2: OPV model with insufficient vaccination ($p = 0.1$)

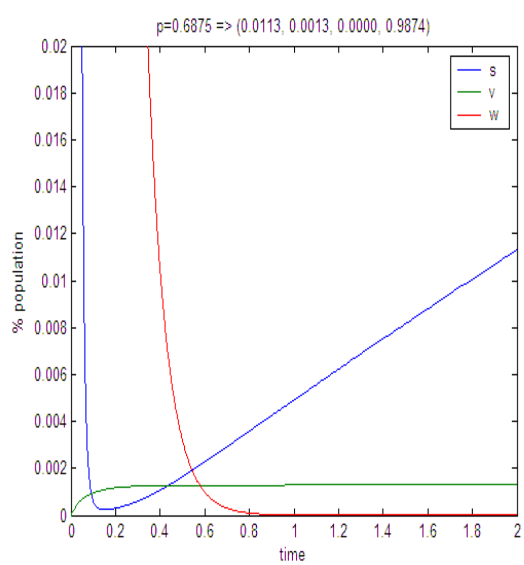

Figure 3: OPV model with $p = p^* = 0.6877$

parameter	value
μ	1/45
β_v	36
β_w	144
γ_v	12
γ_w	12

2.2 The IPV Model

The IPV model provided by Eichner and Hadeler [4] considers five sub-populations of a constant population. The fraction of the population that has not been vaccinated or infected is the "original" susceptible population, s_0. The fraction of the population that has been vaccinated, but are not completely immune due to the ineffectiveness of the IPV vaccine, is the reduced susceptibility population (assumed to be homogenous), s_1. The fraction of the population that has contracted the wild-poliovirus, and was never vaccinated, are the "original" infecteds, w_0. The fraction of the population that has contracted the wild-poliovirus after having been vaccinated are in class w_1. Those who have gained full immunity to the poliovirus are in the removed population, r. The model is as follows:

$$\dot{s_0} = \mu(1-p) - \beta(w_0 + gw_1)s_0 - \mu s_0 \quad (13)$$

$$\dot{s_1} = \mu(1-a)p - \beta(w_0 + gw_1)fs_1 - \mu s_1 \quad (14)$$

$$\dot{w_0} = \beta(w_0 + gw_1)s_0 - (\gamma + \mu)w_0 \quad (15)$$

$$\dot{w_1} = \beta(w_0 + gw_1)fs_1 - \left(\frac{\gamma}{h} + \mu\right)w_1 \quad (16)$$

$$\dot{r} = \gamma\left(w_0 + \frac{w_1}{h}\right) - \mu r + \mu ap. \quad (17)$$

Again, the authors assume a constant population with birth rate = death rate = μ, and that a fraction p of the new births are vaccinated, but due to the ineffectiveness of the vaccine, only a fraction a of these enter the removed population. The "original" infected population (w_0) will infect the "original" susceptible population (s_0) at a rate β, but the infectivity of the vaccinated infected population (w_1) is reduced by a factor g ($0 \leq g \leq 1$), and the susceptibility of the vaccinated susceptible population by a factor f, $0 \leq f \leq 1$. The "original" infected population will recover at a rate γ, but vaccination increases the recovery rate by a factor $\frac{1}{h}$ ($0 < h \leq 1$).

Similar to above, we can find the basic reproductive numbers, R_0 and R_1, of the w_0 and

w_1 populations (resp.) and find

$$R_0 = \frac{\beta}{\gamma + \mu} \tag{18}$$

$$R_1 = \frac{\beta f g}{\gamma/h + \mu}. \tag{19}$$

We note again that in general, both R_0 and R_1 are both greater than 1, hence the virus is endemic. We can find the uninfected equilibrium by setting $w_0 = w_1 = 0$ and solving the system for $(\bar{s}_0, \bar{s}_1)$ (note that since we have a constant population $s_0 + s_1 + w_0 + w_1 + r = 1$, thus we need only consider the system (s_0, s_1, w_0, w_1)). We find the uninfected equilibrium to be

$$\bar{s}_0 = 1 - p \tag{20}$$

$$\bar{s}_1 = (1 - a)p. \tag{21}$$

Since it is assumed that we are not yet on a trajectory toward the uninfected equilibrium, Eichner and Hadeler prove the proposition that at a vaccination level p, the basic reproduction number for the virus is $R(p) = R_0 - (R_0 - (1-a)R_1)p$. Given that this is true (see paper for proof), we can set $R(p) = 1$ and solve for the critical value $p = p^*$ such that for all $p > p^*$, the average infected person is infecting less than one other person, hence the virus will die out. They find

$$p^* = \left(1 - \frac{1}{R_w}\right) \frac{R_w}{R_w - (1-a)R_1}. \tag{22}$$

2.2.1 IPV Simulations

For the system of five differential equations representing IPV vaccination dynamics, we use Matlab to integrate the equations with both a stiff and non-stiff solver (ode15s and ode45, resp.) with the absolute and relative tolerance set to $1e-10$ (parameter values can be found at the end of this section). It shall just be noted that the system was more efficient with the non-stiff solver, and hence it is assumed that this is a non-stiff system.

After substituting parameter values for an arbitrary developing country (found in [4] and listed below), we find the basic reproductive numbers and critical vaccination level as follows:

$$R_0 = 11.98$$

$$R_1 = 1.199$$

$$p^* = 0.9856.$$

It should be noted that the value for p^* is very high, but not unrealistically so. For example, in Bosnia, for the first three boosters of Polio vaccine, 99 percent of children received the first dose by the age of 12 months and this only declines to 96 percent by the third dose [1], thus vaccinating at the 98.56% is possible.

In the absence of vaccination, there is again oscillations in the trajectories of the populations (see figure 4). At the 10% vaccination level, we see oscillations again, but the infected

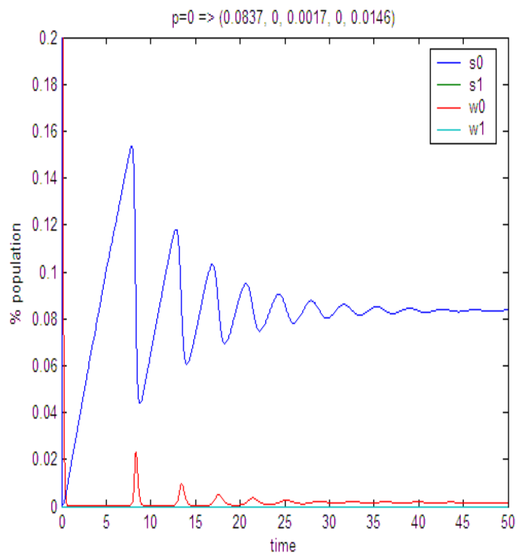

Figure 4: IPV model in the absence of vaccination ($p = 0$)

populations settle at a lower level (see figure 5). When $p = p^* = 0.9856$, we see that w_0 and w_1 approach zero relatively quickly (see figure 6). This again indicates that the model may be insufficient, since it is unlikely that vaccinating the new births will eradicate polio so fast.

parameter	value
μ	1/45
a	0.3
β	144
γ	12
f	0.5
g	1
h	0.2

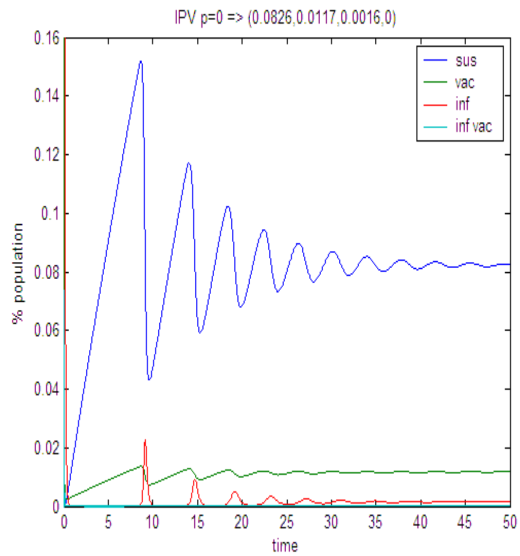

Figure 5: OPV model with insufficient vaccination ($p = 0.1$)

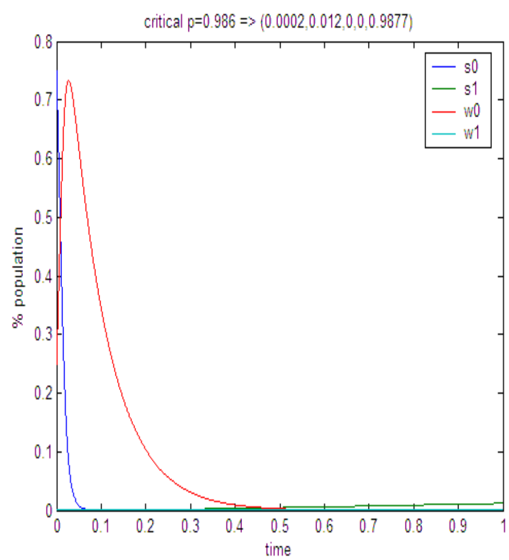

Figure 6: IPV model with $p = p^* = 0.9856$

3 Optimal Control

In the 1950s, L.S. Pontryagin and a team of mathematicians developed what is called the maximum principle, which gives equivalent results to the problems addressed under the classical calculus of variations, but is also capable of handling such things as constraints on derivatives of functions (which is useful in economics where net investment and production rates are nonnegative) [7].

In general, every optimal control problem requires a set of state variables ($x(t)$) whose dynamics are determined by a set of differential equations ($\frac{dx_i}{dt} = f_i(x,t)$). The goal of optimal control theory is regulate one or more of the state variables by deriving a set of control functions, $u(t)$, which are incorporated into the system of differential equations. These control functions are to be chosen such that the state is controlled optimally. To do this we first need a quantitative way of measuring the state and "cost" of using the control. We do this by establishing an objective functional, $J(x, u(t), t)$, which is to be minimized subject to the given constraints of the state variables. Since this theory was first applied within the context of economics, this objective functional is also known as the "cost function".

3.1 Optimally Controlling the OPV Model

Our goal is to drive v and w to zero optimally. The only component of the system that we can control is the vaccination level, p, thus consider our control $p = p(t)$. We then have as our system:

$$\dot{s} = (1 - p(t))\mu - \beta_w sw - \beta_v sv - \mu s \tag{23}$$

$$\dot{v} = p(t)\mu + \beta_v sv - \gamma_v v - \mu v \tag{24}$$

$$\dot{w} = \beta_w sw - \gamma_w w - \mu w \tag{25}$$

$$\dot{r} = \gamma_w w + \gamma_v v - \mu r \tag{26}$$

Consider the cost function:

$$\min_{p \in \Omega} \int_{t_0}^{t_1} \frac{1}{2}Av^2 + \frac{1}{2}Bw^2 dt \tag{27}$$

where A and B are weighted parameters.

We then must construct the Hamiltonian, H (as described by Kamien and Schwartz in [7]:

$$H = \frac{1}{2}Av^2 + \frac{1}{2}Bw^2 + \lambda_1\dot{s} + \lambda_2\dot{v} + \lambda_3\dot{w} + \lambda_4\dot{r} \tag{28}$$

where each λ_i, $i = 1,\ldots,4$ satisfy the following costate equations:

$$\dot{\lambda}_1 = -\frac{dH}{ds} = \lambda_1(\beta_w w + \beta_v v + \mu) - \lambda_2\beta_v v - \lambda_3\beta_w w \quad (29)$$

$$\dot{\lambda}_2 = -\frac{dH}{dv} = -Av + \lambda_1\beta_v s - \lambda_2(\beta_v s - \gamma_v - \mu) - \lambda_4\gamma_v \quad (30)$$

$$\dot{\lambda}_3 = -\frac{dH}{dw} = -Bw + \lambda_1\beta_v s - \lambda_3(\beta_w s - \gamma_w - \mu) - \lambda_4\gamma_w \quad (31)$$

$$\dot{\lambda}_4 = -\frac{dH}{dr} = -\lambda_4 r. \quad (32)$$

Pontryagin's Maximum Principle states that in order for $p^*(t)$ to be optimal, it is necessary that H be at a minimum at $p^*(t)$, hence we must have

$$\frac{dH}{dp} = \lambda_1\mu - \lambda_2\mu = 0. \quad (33)$$

Since the derivative is not a function of p, we have can only have a bang-bang solution (i.e. the control will either be at its maximum or minimum). Since we must force $\frac{\partial H}{\partial t} = 0$, $p^*(t) = p_{max}$ when $\mu(\lambda_1 - \lambda_2) < 0$ and $p^*(t) = 0$ when $\mu(\lambda_1 - \lambda_2) > 0$. At $\mu(\lambda_1 - \lambda_2) = 0$ we define $p^*(t) = 0.5$, between p_{min} and p_{max}.

We then must impose transversality conditions on the costate variables to make this problem well-posed. The transversality conditions (as outlined in [7]) are as follows: $(\lambda_1(t_f), \lambda_2(t_f), \lambda_3(t_f), \lambda_4(t_f))$ $(0,1,1,0)$ (since we want the vaccinated and infected populations to tend toward zero, and the remaining two populations are free at the final time). Since we have initial conditions for the state variables and terminal conditions on the costate variables, but must solve the entire system over the entire time interval simultaneously, we have a two-point boundary value problem (TPBVP). I chose to use Newton's method to solve the TPBVP, and we shall discuss Newton's method in more detail presently. Let $q = \lambda_0 = \lambda(0)$ be the parameter representing the set of initial conditions for the costate equations, and let G be a map such that $G(q) = \lambda(T) - \lambda_\infty$, where λ_∞ is the desired terminal value of the costate equations (in this case, $\lambda_\infty = (0,1,1,0)$). Our goal is to find q such that $G(q) = 0$. To find such a q, we construct a sequence $q_{n+1} = q_n - J(q_n)^{-1}G(q_n)$ where $J(q_n)^{-1}$ is the inverse of the Jacobian matrix (determined from the variational equation $\frac{d}{dt}\frac{\partial x}{d\lambda} = \frac{\partial}{\partial\lambda}\frac{dx}{dt} = \frac{\partial}{\partial\lambda}f(x,u(t))$). Within the context of a computer program, one terminates the sequence when $G(q_n)$ is sufficiently close to 0.

The results of the simulation is in figure 7. I have chosen $p_{max} = 0.9$ since that is a realistic goal for a series of NIDs, which the bang-bang solution seems to represent. One will notice that the trajectory of the infected population does not seem to deviate from that of the previous model. This is interesting because under the optimal vaccinations, we are not constantly vaccinating (which is not always possible in developing countries due to the insufficient staff required for such goals, but it is possible to build up the required number of volunteers for NIDs).

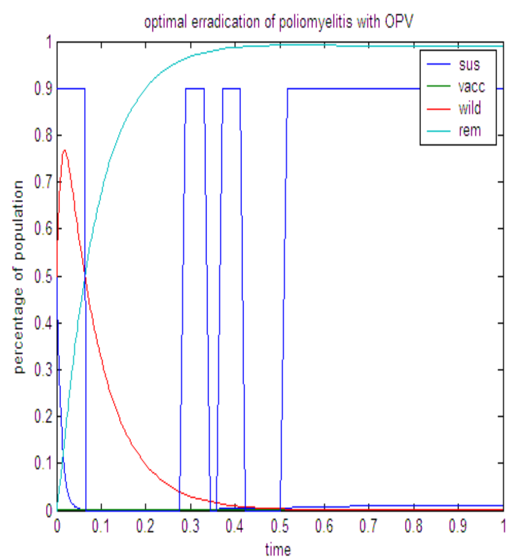

Figure 7: optimal vaccinations for OPV model

3.2 Optimally Controlling the IPV Model

In this section, we apply the same optimal control theory of the previous section to the IPV model. Recall that the set of state equations are as follows:

$$\dot{s_0} = \mu(1 - p(t)) - \beta(w_0 + g w_1)s_0 - \mu s_0 \quad (34)$$

$$\dot{s_1} = \mu(1 - a)p(t) - \beta(w_0 + g w_1) f s_1 - \mu s_1 \quad (35)$$

$$\dot{w_0} = \beta(w_0 + g w_1)s_0 - (\gamma + \mu)w_0 \quad (36)$$

$$\dot{w_1} = \beta(w_0 + g w_1) f s_1 - \left(\frac{\gamma}{h} + \mu\right) w_1 \quad (37)$$

$$\dot{r} = \gamma\left(w_0 + \frac{w_1}{h}\right) - \mu r + \mu a p(t). \quad (38)$$

Our goal is to bring the infected populations to zero, and our only control is vaccination. We seek to find the function $p(t) = p^*(t)$ that will bring the infected populations to zero optimally. In line with the typical optimal control theory outlined above, we shall establish an objective function that quantifies the cost of the virus which we will minimize. Consider the following as out objective functional:

$$J = \int_{t_0}^{t_1} \frac{1}{2}Aw_0 + \frac{1}{2}Bw_1 dt. \tag{39}$$

We can then construct our Hamiltonian based on the theory of Kamien and Schwartz [7]:

$$H = \frac{1}{2}Aw_0^2 + \frac{1}{2}Bw_1^2 - \vec{\lambda} \cdot \dot{x} \tag{40}$$

where we denote (s_0, s_1, w_0, w_1, r) as $(x_1, x_2, x_3, x_4, x_5) = \dot{x}$ and define $\vec{\lambda}$ as the set of costate variables which satisfy the following differential equations:

$$\dot{\lambda}_1 = -\frac{dH}{dx_1} = \lambda_1(\beta(x_3 + gx_4) + \mu) - \lambda_3\beta(x_3 + gx_4) \tag{41}$$

$$\dot{\lambda}_2 = -\frac{dH}{dx_2} = \lambda_2(\beta(x_3 + gx_4)f - \mu) - \lambda_4\beta(x_3 + gx_4)f \tag{42}$$

$$\dot{\lambda}_3 = -\frac{dH}{dx_3} = \lambda_1\beta x_1 + \lambda_2\beta f x_2 - \lambda_3(\beta - (\gamma + \mu)) - \lambda_4\beta - \lambda_5\gamma \tag{43}$$

$$\dot{\lambda}_4 = -\frac{dH}{dx_3} = \lambda_1\beta g x_1 + \lambda_2\beta g f x_2 - \lambda_3\beta g x_1 \tag{44}$$

$$- \lambda_4 \left(\beta g f x_1 - \frac{\gamma}{h} - \mu \right) - \frac{\gamma}{h}\lambda_5 \tag{45}$$

$$\dot{\lambda}_5 = -\frac{dH}{dx_5} = \lambda_5\mu. \tag{46}$$

One necessary condition for an optimal $p^*(t)$ is that the Hamiltonian be constant with respect to the control at the optimum, hence

$$\frac{dH}{dp} = -\mu(\lambda_1 - a\lambda_2)p = 0. \tag{47}$$

Since the derivative of the Hamiltonian with respect to p is not a function of p, we have only a bang-bang solution, hence we will jump from p_{min} to p_{max} at discrete times.

The results of this simulation can be found in figure 8. I chose to use $p_{max} = 0.9$ again, since this is a reasonable goal. Notice in this case that the vaccinations are constant for the first 0.3 of the year, and zero past that. This indicates that although a higher vaccination level over the entire period is required to guarantee eradication, less eradication for an optimal amount of time can also drive the infected population toward zero.

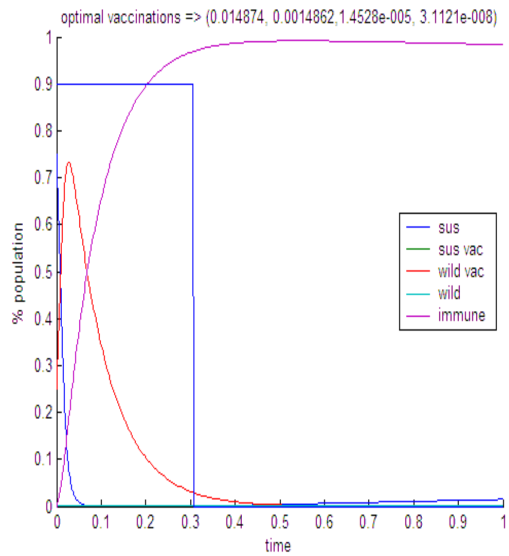

Figure 8: optimal vaccinations for IPV model

4 Conclusion

For this project, I started out on a quest to optimally eradicate polio. Along the way, I found the models that I was soon to subject to the theory of optimal control. Upon doing so, I was able to derive the abstract form for the optimal vaccination strategy for any given country, and hence develop a qualitative understanding of the relationship between optimal vaccination and the mathematics. However, since the system was multi-dimensional and nonlinear, there was no way to solve the two-point boundary value problem analytically. I was therefore required to subject this abstract system to Newton's method for a numerical approximation. Thankfully I was able to get Newton's method to converge. I am aware that this is not always the case.

As a way of furthering this research, it would always to be nice to experiment with various other forms of the objective functional. With each different objective functional, one will achieve slightly different results, and hence it would be worthwhile to experiment with various other forms. For example, I chose to use a quadratic form for the populations that I was seeking to minimize, but it would be interesting to see how a linear form would differ. It would also be nice to have a model which could incorporate dynamics of both IPV and OPV vaccinations. A very good optimal control problem could then be set up to optimally choose what percentage of the population should be vaccinated with IPV and what percent should be vaccinated with OPV (given the associated costs and benefits of each vaccine).

References

[1] A World Without Polio. May 1, 2003. UNICEF. <http://www.unicef.org/polio/>

[2] Cvjetanovic, B., Grab, B., Dixon, H. Epidemiological models of poliomyelitis and measles and their application in the planning of immunization programmes. Bull. WHO. 60:405-22(1982.

[3] Debanne, SM., Rowland, DY. Statistical certification of eradication of poliomyelitis in the Americas. Mathematical Biosciences 150:83-103(1998)

[4] Eichner, M., Hadeler, K.P. Deterministic Models for the Eradication of Poliomyelitis: Vaccination with the Inactivated (IPV) and Attenuated (OPV) Polio Virus Vaccine. Mathematical Biosciences 127:149-166 (1995)

[5] Eichner, M., Dietz, K. Eradication of Poliomyelitis: When Can One be Sure That Poliovirus Transmission Has Been Terminated? American Journal of Epidemiology 143:816-22(1996).

[6] Hull, HF., Aylward, RB. Invited Commentary: The Scientific Basis for Stopping Polio Immunization. American Journal of Epidemiology. 150:1022-5(1999).

[7] Kamien, M.I., Schwartz, N.L. Dynamic Optimization: The Calculus of Variations and Optimal Control in Economics and Management. vol. 4. North Holland. New York. 1981.

[8] Miner, R.W. (ed.) Biology of Poliomyelitis. Annals of the New York Academy of Sciences. 61:737-1064(1995)

[9] Oldstone, M.B.A. Viruses, Plagues, and History. Oxford University Press. New York. 1998.

[10] Smallpox Eradication – A Global First. May 1, 2003. WHO. <http://www.who.int/archives/who50/en/smallpox.htm>

[11] The End of Polio. May 1, 2003. End of Polio. <http://www.endofpolio.org>