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Optimal Chemotherapy Strategies in an Existing HIV Model

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I have reviewed this completed senior honors thesis with this student and certify that it is a project commensurate with honors level undergraduate research in this field.

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ABSTRACT

Mathematical models are often used in describing immune response to HIV infection, and treatment against HIV infection can be improved through the study of these descriptions. One such model from Kirschner and Webb's paper, "Immunotherapy of HIV-1 Infection," uses a system of two differential equations to model the interaction of the AIDS virus and CD4+ T-cells. Beginning with this existing model, we modify the equations to include the mathematical representation of a theoretical antiviral treatment based on maximizing the benefit to the patient. Solving this problem requires both analytic and numerical evaluations, and a numerical example is provided to illustrate the form of a treatment schedule. In solving the optimal control problem we learn how to best administer such a treatment to extend the life of the patient.

I. Introduction:

Mathematical models provide great insight into the workings of many biological environments. Quantifying the living world helps in the understanding of the dynamics within organisms and assists in medical studies, environmental studies, and other areas of biological benefit. In medicine specifically, mathematical models can represent the actions of disease, and medical researchers can find optimal ways of treating infection through the use of such models. By the understanding of the dynamics of the immune system and its responses, the study of medicine can advance in efficiency of treatments.

Many different researchers have considered the immune system's mathematical basis, recognizing the potential for describing immune cell numbers in terms of simple population models. When infectious cells, viruses, bacteria, etc., enter the body, the relationship between immune cells and invading cells becomes much like a predator-prey relationship. When the body becomes infected with the Human Immunodeficiency Virus, however, the system immediately becomes more complicated. Many researchers and mathematicians have dealt with the topic of HIV infection described through mathematical modeling, and hopefully their work will help in the treatment of the terminal disease. The different models have their own advantages and disadvantages so one model will not necessarily lead to the "cure" for HIV infection. Through the study of these models, researchers can continually make improvements to the existing systems and hopefully achieve the best treatment possible.

Control theory is the mathematical study of adjusting features of systems to achieve desired goals. When relating control theory to medical models such as those involving HIV infection, we must consider the patient's threshold for treatment while we strive for the highest

achievable results of patient benefit (Fleming 2). Using an existing model from "Immunotherapy of HIV-Infection" (Kirschner 73-74), we mathematically controlled the system in order to find the best way to administer a certain type of treatment for the infection. The theoretical treatment used in this evaluation fights HIV by inhibiting the proliferation of virus particles by infected T-cells. By using control theory, we hoped to find an analytical/numerical representation of treatment that maximizes benefit to the patient.

II. Existing HIV Modeling

Mathematical models of HIV infection vary in many respects, but all basically begin with the underlying idea somewhat similar to a predator-prey or competition relationship. Because HIV infects immune cells themselves, the relationship between T-cells and HIV becomes very complicated. HIV models have many factors to consider, and some models involve several equations. One system from "Mathematical Analysis of Antiretroviral Therapy Aimed at HIV-1 Eradication or Maintenance of Low Viral Loads" models HIV infection with a ten differential equation model (Wein 83). Models of HIV infection range from highly complex to fairly simple, varying in assumptions and in the populations considered.

The majority of mathematical models of viruses concern HIV-1, for HIV-1 is the most studied human virus (Regoes 451). As stated in "Virus Dynamics: the Effect of Target Cell Limitation and Immune Responses on Virus Evolution," seven assumptions underlie the theory of HIV-1 progression. These assumptions are

> (I) virus load causes disease; (ii) immune responses reduce virus load; (iii) HIV-1 can impair immune responses by killing CD4 cells; (iv) there is continuous and rapid virus replication throughout the course of infection; (v) the rapid turnover

> leads to a large number of virus mutants; (vi) some of these mutants can escape from immune responses; (vii) the virus may evolve towards faster replication rates during infection (451-452).

Although not all models incorporate mutations, these assumptions relate the basic idea of the situation being modeled.

One specific model of the dynamics of HIV infection is "Immunotherapy of HIV-1 Infection" by D.E. Kirschner and G.F. Webb. This paper assesses the benefit of using interleukins, a specific type of cytokine, to boost the immune response to the infection (Kirschner 71). Kirschner and Webb model the immune response to HIV-1 infection using only the populations of virus particles and of T-cells. They do not use different states of the T-cells (e.g., infected and latent, infected and actively producing virus), and hence their model is relatively simple in comparison to many other existing models. Kirschner and Webb's work resulted in the two equation system of ordinary differential equations,

$$\frac{dT}{dt} = s1 - \frac{(s2)V}{(b1 + V)} - \mu T - kVT$$

$$\frac{dV}{dt} = \frac{gV}{(b2 + V)} - cVT \quad ,$$

in which T represents the concentration of CD4+ T-cells as a function of time and V represents the concentration of free virus particles as a function of time. The first two terms of dT/dt represent the source and proliferation of healthy CD4+ T-cells and s1=20 and s2=1.5. The values b1 and b2 are half saturation constants and they equal 14.0 and 1.0, respectively. The value $-\mu T$ is a natural death term and -kVT involves the loss of T-cells to viral infection. The value μ, death rate of uninfected T-cells, is 0.002; and k, the rate of infection by free virus, is 2.5*10^-4. The

term gV/(b2 + V) involves virus proliferation from several areas other than plasma such as the lymph system. The value g, input rate of external viral source, is 30. The initial value for T for the model is 1000.0, but three different values in different versions of the paper are listed for initial V: 1.0, 1000, 3000. The model is fundamentally a modified predator-prey or (more accurately) competition relationship with interaction terms of -kVT and -cVT. (In their paper, Kirschner and Webb further modified the system with a drug input function r(t) representing the interleukin treatment by adding the term r(t)T to the dT/dt equation.)

III. Implementation of the Antiviral Function

The original system devised by Kirschner and Webb was re-evaluated in its original form and modified to include an antiviral treatment inhibiting the production of virus particles. Using control theory, the optimal treatment schedule can be calculated for this treatment. Because the treatment affects virus proliferation, the effect of the control function u(t) is the coefficient of the proliferation term for the virus population. For controls u(t) such that $.1 < u(t) < .9$, our state system is

$$\frac{dT}{dt} = 2.0 - \frac{1.5V}{(14.0 + V)} - .002T - (2.5*10\text{^}(-4))VT$$

$$\frac{dV}{dt} = \frac{30V(\ .9-u(t)\ )}{(1.0 + V)} - .007VT \ .$$

IV. Evaluation of the System

When creating the best situation for the patient, we must consider both the positive and

negative results of the treatment. In order to maximize the benefit to the patient, we must maximize the objective functional,

$$\int_0^{t1} (T(t) - (\tfrac{1}{2})\beta u^2(t))\, dt \quad ,$$

which represents the benefit to the immune system through increased concentration of T-cells minus the systemic cost of the treatment. By finding u*(t), the optimal treatment which maximizes this integral, we find the treatment schedule which provides the greatest overall benefit to the patient. When maximizing this integral, we must first find and utilize the Hamiltonian of the system,

$$H = (T-(\tfrac{1}{2})\beta u^2(t)) + \lambda 1(dT/dt) + \lambda 2(dV/dt),$$

where $\lambda 1$ and $\lambda 2$ are functions dependent on values of T, V, and time (Kamien 124-128). Solving the optimality equation, $\partial H/\partial u = 0$, gives the optimal equation for the treatment,

$$u^*(t) = \begin{cases} 0.1 & u < 0.1 \\ \dfrac{-\lambda 2 * 30V}{\beta*(1.0+V)} & 0.1 < u < 0.9 \\ 0.9 & u > 0.9 \end{cases} .$$

The adjoint equations, $\lambda 1' = (-\partial H/\partial T)$ and $\lambda 2' = (-\partial H/\partial V)$, evaluated from the Hamiltonian are

$$\lambda 1' = \lambda 1*(.002+.007V) + \lambda 2*(2.5*10\text{^}(-4)V - 1.0$$

$$\lambda 2' = \lambda 1*\left(\frac{21.0}{(14.0+v)^2} + (2.5*10\text{^}(-4))T \right) - \lambda 2*\left(\frac{27.0-30u}{(1.0+v)^2} - .007T \right)$$

which are necessary in finding the numerical solution of the modified system. To determine if these equations do in fact produce a maximum value for the functional, we must verify that the second partial derivative of the Hamiltonian with respect to u*(t) is negative. We find that $\partial^2 H/\partial u^2 = -\beta$; therefore, choosing $\beta>0$ will make u*(t) the optimal treatment function.

Solving the model itself must be done numerically. The original model was re-solved using the classic Fourth Order Runge-Kutta method written in a Fortran code (Appendix A). The values of the T-cells decrease and the values of the virus increase so quickly initially that an extremely small step-size must be used or the values will become negative. The initial concentration of T-cells, T0, was set at 500.0 in the newly modified system rather than T0=1000.0 as in the original paper. The initial value was lowered in order to simulate a later stage of infection. The original model lists three initial values for the virus population in two different copies of the paper (one copy prior to publication), but the value 1000.0 was used in this evaluation because this value was included in the actual published result and the re-evaluation results seemed logical. The value $\beta=124.0$ was chosen because it provided the best results and did not violate the condition $\beta>0$. The optimality system, which is the original T(t) and V(t) ODEs coupled with adjoint ODEs including the control u*(t), was evaluated using an iterative method with the Classic Fourth Order Runge-Kutta Method in a FORTRAN code (Appendix B). Numerical solutions were found for the resulting functions of the T-cell population with respect to time, the virus population with respect to time, as well as the treatment schedule over time. The numerical results for the original system and the optimized system were computed in the respective FORTRAN codes then graphed using MATLAB.

V. Results and Discussion

The virus population values decrease in the presence of treatment (Figure 1 and Figure 2) although the results do not appear to be drastic. The numerical results to the original system show a steady decline in the T-cell population (Figure 3), but the population of the T-cells behaves quite differently in the presence of treatment. The positive change in T-cell numbers in the presence of treatment is quite obvious (Figure 4), with T-cell numbers increasing over the majority of the treatment period and gradually declining near the end of the treatment period. Hence, the treatment schedule does appear to increase the T-cell population over the course of treatment and therefore seems to benefit the patient. The numerical results for $u^*(t)$, the treatment schedule (Figure 5). includes high levels of treatment at the beginning of the treatment period with the dosage decreasing over the course of treatment. This result suggests that an intense treatment is very beneficial initially in the treatment schedule, but maintaining that strength of treatment would not result in the overall best situation for the patient. Most likely the negative effects of the drug outweigh the benefits of high treatment levels as time progresses.

Although the treatment discussed here is theoretical, current treatments exist inhibiting different stages of HIV infection which affect the progression of the disease in various major ways, including the prevention of binding of HIV to the surface of the host cell and the inhibition of reverse transcription of RNA from the HIV particle into T-cell DNA. The treatment evaluated in this paper is assumed to treat through inhibition of one or more stages of viral production. The combined use of different treatments, i.e., a "drug cocktail," has the potential for highly favorable results. By using optimal treatment schedules, we can best combine these various treatments to

benefit patients.

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Wein, Lawrence M., et al. "Mathematical Analysis of Antiretroviral Therapy Aimed at HIV-1 Eradication or Maintenance of Low Viral Loads." Journal of Theoretical Biology 192 (1998): 81-98.

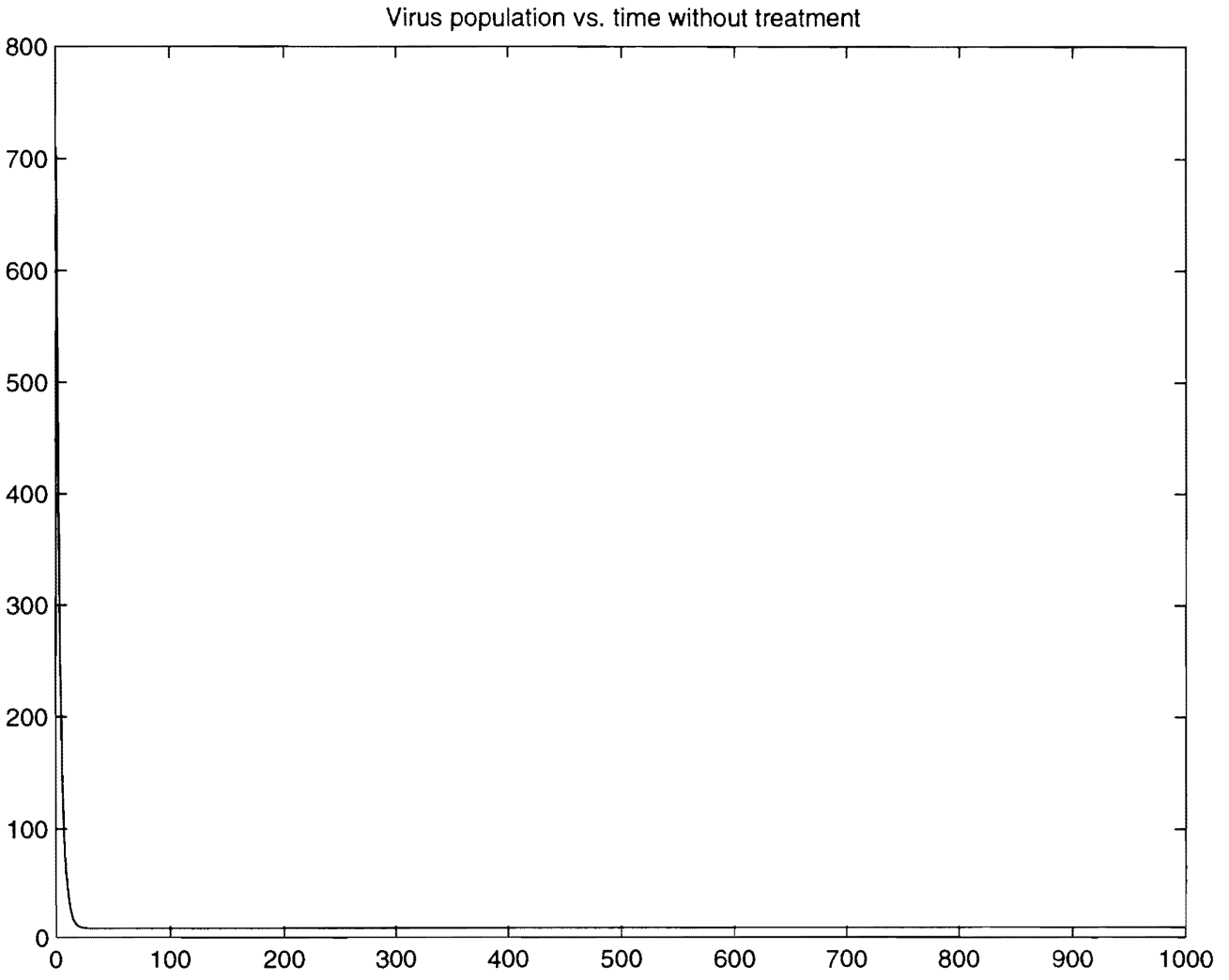
Virus population vs. time without treatment
800
700
600
500
400
300
200
100
0
0
100
200
300
400
500
600
700
800
900
1000

Figure 1

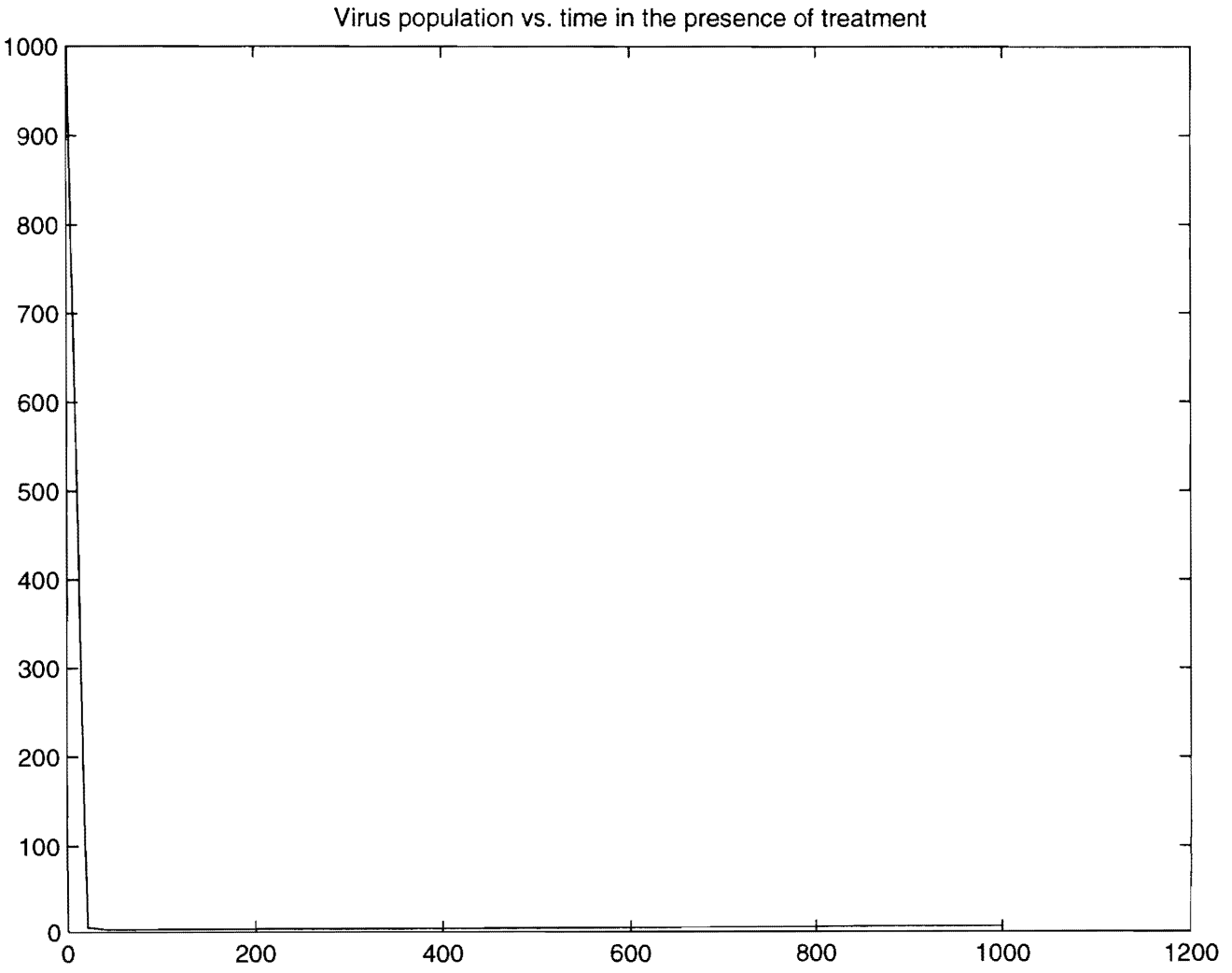
Virus population vs. time in the presence of treatment
1000
900
800
700
600
500
400
300
200
100
0
0
200
400
600
800
1000
1200

Figure 2

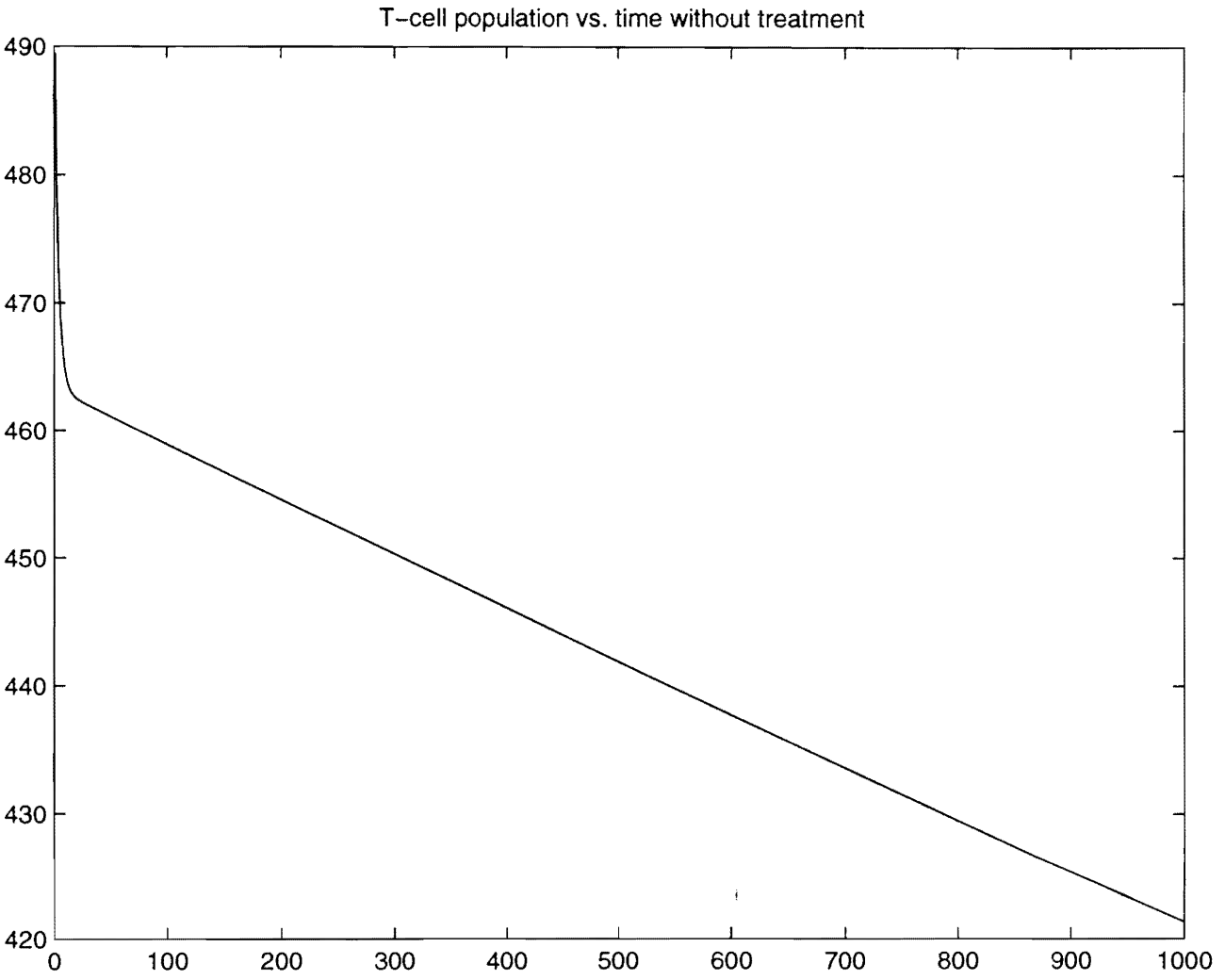
T-cell population vs. time without treatment
490
480
470
460
450
440
430
420
0
100
200
300
400
500
600
700
800
900
1000

Figure 3

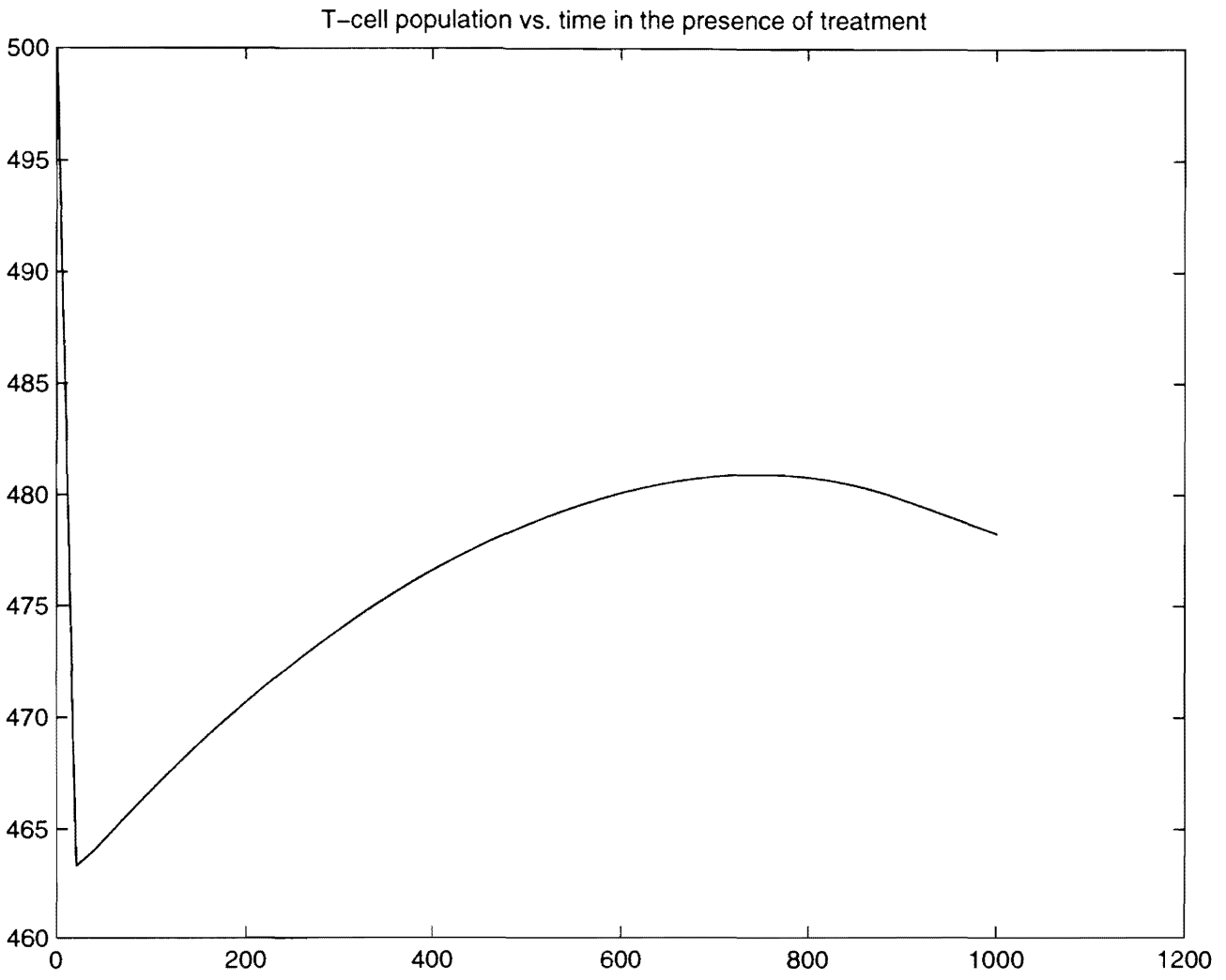
T-cell population vs. time in the presence of treatment
500
495
490
485
480
475
470
465
460
0
200
400
600
800
1000
1200

Figure 4

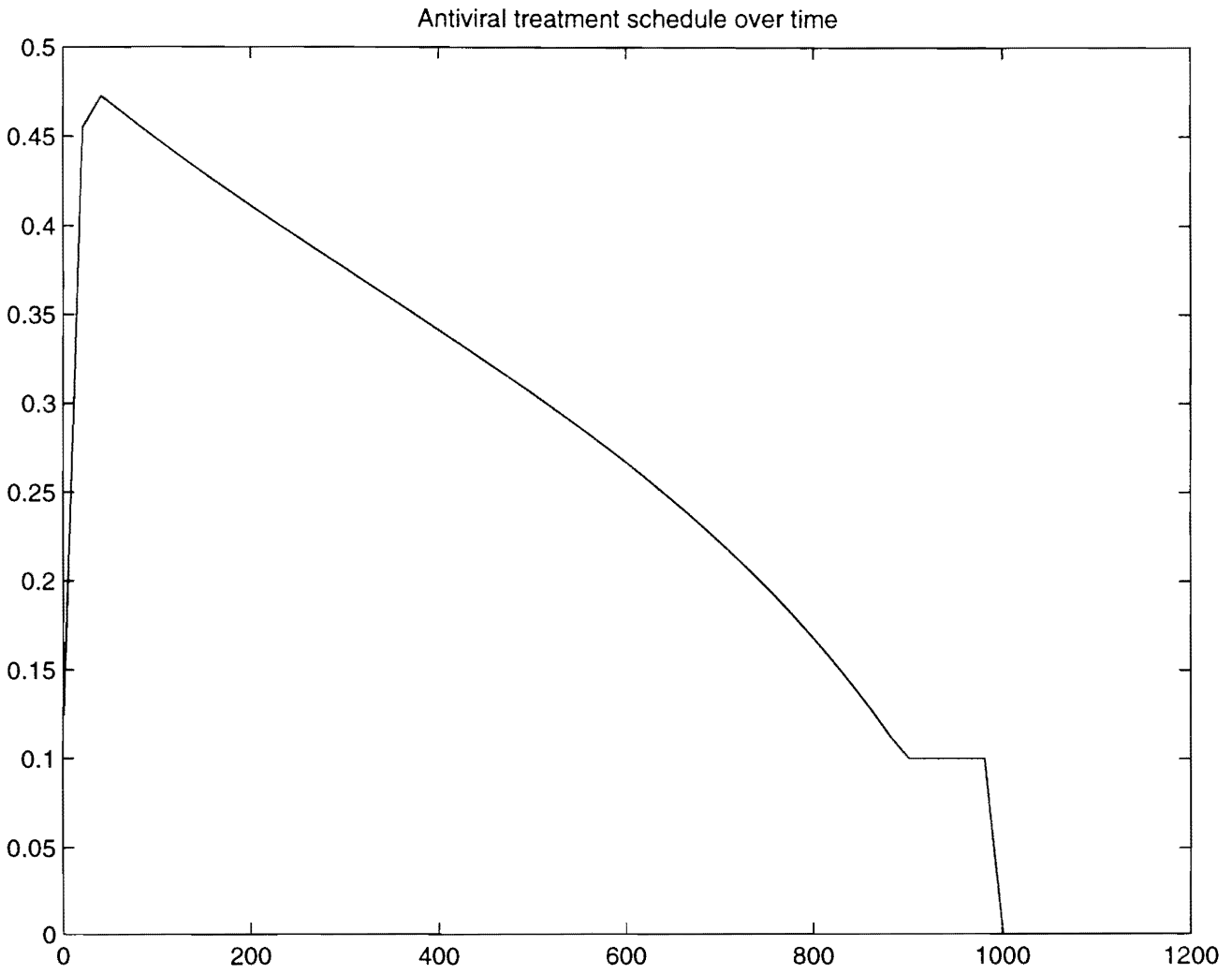
Antiviral treatment schedule over time
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
200
400
600
800
1000
1200

Figure 5

Appendix A

```
c This program solves a system of differential equations modeling
c the action of the immune system in response to HIV infection.  The
c model comes from "Immunotherapy of HIV-1 Infection," D.E. Kirschner
c and G.F. Webb, Journal of Biological Systems.

      implicit none
      real ti, tf, h, t, v
      integer n, i
      real xn(2,1001), x1, x2, kx(2,4)

c The original differential equations are entered:

      x1(t,v) = 2.0 - (1.5*v)/(14.0+v) - .002*t - (2.5e-4)*v*t
      x2(t,v) = 30.0*v/(1.0+v) - .007*v*t

c Initialize values:

      n = 1000
      ti = 0.0
      tf = 100.0
      h = (tf-ti)/n

c Initial values are set for the loop:

      xn(1,1) = 500.0
      xn(2,1) = 1000.0

c Begin the loop using R-K:

      DO i=1,n+1

          kx(1,1)=h*x1(xn(1,i),xn(2,i))
          kx(2,1)=h*x2(xn(1,i),xn(2,i))

          kx(1,2)=h*x1(xn(1,i)+kx(1,1)/2,xn(2,i)+kx(2,1)/2)
          kx(2,2)=h*x2(xn(1,i)+kx(1,1)/2,xn(2,i)+kx(2,1)/2)

          kx(1,2)=h*x1(xn(1,i)+kx(1,1)/2,xn(2,i)+kx(2,1)/2)
          kx(2,2)=h*x2(xn(1,i)+kx(1,1)/2,xn(2,i)+kx(2,1)/2)

          kx(1,3)=h*x1(xn(1,i)+kx(1,2)/2,xn(2,i)+kx(2,2)/2)
          kx(2,3)=h*x2(xn(1,i)+kx(1,2)/2,xn(2,i)+kx(2,2)/2)

          kx(1,4)=h*x1(xn(1,i)+kx(1,3),xn(2,i)+kx(2,3))
          kx(2,4)=h*x2(xn(1,i)+kx(1,3),xn(2,i)+kx(2,3))

c Move t and v values forward in time:

          xn(1,i+1)=xn(1,i)+(kx(1,1)+2*kx(1,2)+2*kx(1,3)+kx(1,4))/6
          xn(2,i+1)=xn(2,i)+(kx(2,1)+2*kx(2,2)+2*kx(2,3)+kx(2,4))/6

          print*,i,xn(1,i+1),xn(2,i+1)

      ENDDO
c     print*,xn(1,n+1),xn(2,n+1)
      stop
      end
```

Appendix B

```
c This program solves a system of differential equations modeling
c the action of the immune system in response to HIV infection.  The
c model comes from "Immunotherapy of HIV-1 Infection," D.E. Kirschner
c and G.F. Webb, Journal of Biological Systems.  The original system
c is modified to include a theoretical antiviral chemotherapy
c treatment.

      implicit none
      real ti,tf,h,t,v,adj1,adj2,uavg,xntavg,xnvavg,c
      real beta,eps,tol,epsx1,epsx2,epsy1,epsy2
      integer n,i,counter,L,k,m,j,ii,p,q,s
      real xn(2,1001),yn(2,1001),x1,x2,y1,y2,kx(2,4),ky(2,4)
      real u(1001),xold(2,1001),yold(2,1001)

c The original differential equations are entered:

      x1(t,v) = 2.0 - (1.5*v)/(14.0+v) - .002*t - (2.5e-4)*v*t
      x2(t,v,c) = 30.0*v*(.9-c)/(1.0+v) - .007*v*t
      y1(adj1,adj2,v) = adj1*(.002+.007*v)+adj2*(2.5e-4)*v-1.0
      y2(adj1,adj2,t,v,c) = adj1*((21.0/((14.0+v)*(14.0+v)))+
     !(2.5e-4)*t)-adj2*((27.0-30.0*c)/((1.0+v)*(1.0+v))-.007*t)

c Initialize values:

      n = 1000
      ti = 0.0
      tf = 100.0
      h = (tf-ti)/n
      beta = 124.0
      tol = 10.0

c Initial values are set for the loops:

      xn(1,1) = 500.0
      xn(2,1) = 1000.0
      DO j=1,n
         yn(1,j)=1.0
         yn(2,j)=-1.0
      ENDDO

      yn(1,n+1)=0.0
      yn(2,n+1)=0.0

c Initialize "old" values to be compared to xn,yn:

      DO m=1,n+1
         xold(1,m)=500.0
         xold(2,m)=1000.0
         yold(1,m)=1.0
         yold(2,m)=1.0
      ENDDO

c Begin the loop using R-K:

      counter=0
25    counter=counter+1
      DO i=1,n

c Here, need to add small loop for u bdd by M:

         u(i)=((-1.0)*yn(2,i)*30.0*xn(2,i))/(beta*(1.0+xn(2,i)))
         if(u(i) .lt. .1) then
            u(i)=.1
         elseif(u(i) .gt. .9) then
            u(i)=.9
```

```
          endif

          uavg=(u(i) + u(i+1))/2.0

          kx(1,1)=h*x1(xn(1,i),xn(2,i))
          kx(2,1)=h*x2(xn(1,i),xn(2,i),u(i))

          kx(1,2)=h*x1(xn(1,i)+kx(1,1)/2,xn(2,i)+kx(2,1)/2)
          kx(2,2)=h*x2(xn(1,i)+kx(1,1)/2,xn(2,i)+kx(2,1)/2,uavg)

          kx(1,3)=h*x1(xn(1,i)+kx(1,2)/2,xn(2,i)+kx(2,2)/2)
          kx(2,3)=h*x2(xn(1,i)+kx(1,2)/2,xn(2,i)+kx(2,2)/2,uavg)

          kx(1,4)=h*x1(xn(1,i)+kx(1,3),xn(2,i)+kx(2,3))
          kx(2,4)=h*x2(xn(1,i)+kx(1,3),xn(2,i)+kx(2,3),u(i+1))

c Move t and v values forward in time:

          xn(1,i+1)=xn(1,i)+(kx(1,1)+2*kx(1,2)+2*kx(1,3)+kx(1,4))/6.0
          xn(2,i+1)=xn(2,i)+(kx(2,1)+2*kx(2,2)+2*kx(2,3)+kx(2,4))/6.0

c         print*,xn(1,i+1),xn(2,i+1)

      ENDDO
c     print*,xn(1,n+1),xn(2,n+1)

c Begin loop for R-K for adjoints:

      DO ii=1,n

c Here, need to add small loop for u bdd by M:

          u(ii)=((-1.0)*yn(2,ii)*30.0*xn(2,ii))/(beta*(1.0+xn(2,ii)))
          if (u(ii) .lt. .1) then
             u(ii)=.1
          elseif (u(ii) .gt. .9) then
             u(ii)=.9
          endif

         L=2+n-ii
         xntavg=(xn(1,L)+xn(1,L-1))/2.0
         xnvavg=(xn(2,L)+xn(2,L-1))/2.0
         uavg=(u(L)+u(L-1))/2.0

         ky(1,1)=-h*y1(yn(1,L),yn(2,L),xn(2,L))
         ky(2,1)=-h*y2(yn(1,L),yn(2,L),xn(1,L),xn(2,L),u(L))

         ky(1,2)=-h*y1(yn(1,L)+ky(1,1)/2,yn(2,L)+ky(2,1)/2,xnvavg)
         ky(2,2)=-h*y2(yn(1,L)+ky(1,1)/2,yn(2,L)+ky(2,1)/2,xntavg,
     !xnvavg,uavg)

         ky(1,3)=-h*y1(yn(1,L)+ky(1,2)/2,yn(2,L)+ky(2,2)/2,xnvavg)
         ky(2,3)=-h*y2(yn(1,L)+ky(1,2)/2,yn(2,L)+ky(2,2)/2,xntavg,
     !xnvavg,uavg)

         ky(1,4)=-h*y1(yn(1,L)+ky(1,3),yn(2,L)+ky(2,3),xn(2,L-1))
         ky(2,4)=-h*y2(yn(1,L)+ky(1,3),yn(2,L)+ky(2,3),xn(1,L-1),
     !xn(2,L-1),u(L-1))

c Move adjoint values in time:

         yn(1,L-1)=yn(1,L)+(ky(1,1)+2*ky(1,2)+2*ky(1,3)+ky(1,4))/6.0
         yn(2,L-1)=yn(2,L)+(ky(2,1)+2*ky(2,2)+2*ky(2,3)+ky(2,4))/6.0

c         print*,yn(1,L+1),yn(2,L+1)
```

```
      ENDDO
c     print*,yn(1,L+1),yn(2,L+1)


c Need to check if control is working as an antiviral:

      epsx1=0.0
      epsx2=0.0
      epsy1=0.0
      epsy2=0.0

      DO p=1,n+1
         epsx1 = epsx1 + abs(xn(1,p)-xold(1,p))
         epsx2 = epsx2 + abs(xn(2,p)-xold(2,p))
         epsy1 = epsy1 + abs(yn(1,p)-yold(1,p))
         epsy2 = epsy2 + abs(yn(2,p)-yold(2,p))
      ENDDO

      eps = epsx1 + epsx2 + epsy1 + epsy2

      if (eps .lt. tol) then
         print*,'convergence after',counter,'iterations'
         print*
         print*,'T-cell:      Virus:       Adj1:       Adj2:        u:'
         DO k=1,n+1,20
            print*,k,' ',xn(1,k),' ',xn(2,k),' ',yn(1,k),' ',yn(2,k),
     !' ',u(k)
         ENDDO
         print*
         print*,'final values:'
         print*,'T-cell:',xn(1,n+1),'Virus:',xn(2,n+1)
         print*,'Adj1:',yn(1,n+1),'Adj2:',yn(2,n+1)
         goto 45

      elseif (counter .gt. 20) then
         print*,'convergence not reached'
         print*,'last values are:'
         DO s=1,n+1,50
            print*,xn(1,k),' ',xn(2,k),' ',yn(1,k),' ',yn(2,k),' ',u(k)
         ENDDO
         print*,'exiting....'
         goto 45

      else
         DO q=1,n+1
            xold(1,q)=xn(1,q)
            xold(2,q)=xn(2,q)
            yold(1,q)=yn(1,q)
            yold(2,q)=yn(2,q)
         ENDDO
         goto 25

      endif


      stop
      end
```