این مقاله در دست نگارش است:

Abstract

A number of treatment strategies are currently being developed to promote antiretroviral therapy-free HIV cure or remission. While complete elimination of the HIV reservoir would prevent recurrence of infection, it is not clear how different remission lengths would affect viral rebound and transmission. In this work, a dynamic model is presented that describes the effect of HIV on the immune system. The effect of introducing antiviral therapy on the model, consisting of RTIs and PIs, along with the outcome of discontinuation of adverse treatment has been investigated. The effect of both drugs can be combined with a single input, which simplifies the model. In addition, the system rotates around a linear equilibrium, leading to a first-order linear differential equation system that can be integrated into control systems engineering courses in higher education.

Keywords:

Modeling, Latency, HIV

Introduction

The acquired immunodeficiency syndrome, which was first recognized in 1981, has spread to over 125 countries and is now considered a critical global health problem. Since the health and socioeconomic consequences of a further rapid spread of AIDS are potentially very serious, there is an urgent need for more accurate forecasts of the future course of the epidemic. HIV (human immunodeficiency virus) is the virus that causes AIDS (acquired immunodeficiency syndrome). By killing or damaging cells of the body's immune system, HIV progressively destroys the body's ability to fight infections and certain cancers. People diagnosed with AIDS may get life-threatening diseases called opportunistic infections, which are caused by microbes such as viruses, bacteria, fungi, or parasites. These infections do not usually make healthy people sick. Those with HIV/AIDS are also at an increased risk of developing certain cancers and a variety of other neurological disorders.

HIV/AIDS is one of the most destructive diseases humankind has ever faced, with profound social, economic and public health consequences. It has become, for three decades, a full-blown pandemic affecting all parts of the world. There are many mathematical models for the behavior of the HIV virus. These models have been used to further study and study the HIV virus as well as its prevalence. Some

of them are for the purpose of analyzing the behavior of the virus by considering the immune system. This study provides an analytical description of a dynamic model for HIV infection.

Mathematical Models of HIV Latency

Viral latency is a major barrier to curing HIV infection with antiretroviral therapy, and consequently, for eliminating the disease globally. The establishment, maintenance, and potential clearance of latent infection are complex dynamic processes and can be best understood and described with the help of mathematical models. Here we review the use of viral dynamics models for HIV, with a focus on applications to the latent reservoir. Mathematical models provide a way to examine the potential effects of the proximate biologic and behavioral determinants of HIV transmission dynamics, alone and in combination. In addition, mathematical models have been used to predict the efficacy of potential HIV cure strategies, such as latency-reversing agents, early treatment initiation, or gene therapies, and to provide guidance for designing trials of these novel interventions. In this project, we will examine the dynamics of HIV latency.

The Immune Deficiency Virus (HIV) attacks the immune system and causes it to decay over time and progressively over the years (if left untreated). The virus can be transmitted mainly through unprotected sexual intercourse. In addition, the virus can be transmitted through needle sharing in drug users and health care incidents, through blood, organs or sperm, and from mother to child during pregnancy or birth.
The virus works by infecting CD4 + T cells. In the early days of the infection, the virus multiplies rapidly, resulting in general symptoms such as the flu for the first 2 to 12 weeks, such as fever, chills, skin rash, night sweats, sore throat, fatigue, and swollen lymph nodes. This stage is called acute HIV infection. The spread of the virus activates the body's immune system to fight infection. This, after a period of 15-12 weeks, suppresses the spread of the virus and stabilizes the immune system. The patient now enters a phase of clinical delay, also called chronic HIV infection. At this stage there is a balance between healthy CD4 + cells and the viral load, so the virus is still active but is suppressed by the immune system and reproduces at a very low level. This stage may last up to 10 years for patients who do not take medication and up to tens of years for patients who are properly prescribed antiviral therapy. Eventually, with chronic deterioration, the immune system becomes weak and vulnerable, making the person vulnerable to opportunistic infections. This is the last stage of HIV infection and is called Acquired Immunodeficiency Syndrome (AIDS). Of course, not all HIV-positive people go this far. Using the cross-pattern of healthy CD4 + T cells, infected CD4 + cells,

and viral load, you can see a simple model that describes the effect of HIV on the immune system. Healthy CD4 cells are produced by the thymus at a constant rate s and die at a rate d. They become infected with the virus at a rate commensurate with their product number and viral load. The effect of infection is exerted by a fixed beta. Infected CD4 + cells are caused by infection of healthy cells and die at a constant rate per square meter. Free virus particles, known as viruses, are produced from infected CD4 + cells at a rate of K and die at a rate of m1.

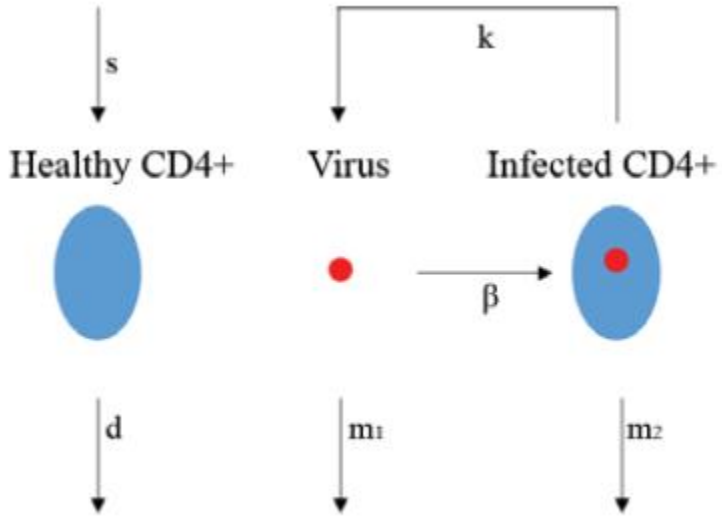

Figure 1. Interaction of HIV and CD4+ cells.

These interactions between healthy CD4 + cells, infected CD4 + and free viruses can be described by a system of nonlinear equations

$$\dot{T}(t) = s - dT(t) - \beta T(t)v(t)$$

$$\dot{T}^*(t) = \beta T(t)v(t) - m_2 T^*(t)$$

$$\dot{v}(t) = kT^*(t) - m_1 v(t)$$

Where T (t) is the healthy number of CD4, T(t) is the number of infected CD4 + and v (t) is the number of viruses, also known as viral load. Typical values of system parameters are given in the table below.

Table 1. Typical values for the system parameters.

t	Time	Days

d	Death rate of uninfected T cells	0.02 per day
k	Rate of virions produced per infected T cell	100 counts/cell
s	Production rate of uninfected T cells	100 mm^3/day
β	Infectivity rate of virions	2.4*$10^{-5} mm^3/day$
m_1	Death rate of virus	2.4/day
m_2	Death rate of infected T cells	0.24/day

Drug categories such as non-nucleoside reverse transcriptase inhibitors (NNRTIs), reverse nucleoside transcriptase inhibitors (NRTIs), and fusion / entry inhibitors. Because most bibliographies, however, focus on RTIs and PIs. RTIs work by blocking infection of new T cells, while PIs prevent the production of new viruses. Due to the effect of these antiviral drugs, the above model is modified:

$$\dot{T}(t) = s - dT(t) - \big(1 - u_1(t)\big)\beta T(t)v(t)$$

$$\dot{T}^*(t) = \big(1 - u_1(t)\big)\beta T(t)v(t) - m_2 T^*(t)$$

$$\dot{v}(t) = \big(1 - u_2(t)\big)kT^*(t) - m_1 v(t)$$

Where$\big(1 - u_1(t)\big)$ and $\big(1 - u_2(t)\big)$ show the effect of RTI and PI, respectively (for $u_{1,2}$ = 0 drug is not injected, while for $u_{1,2}$ = 1 treatment is 100% effective, which of course is not achievable).

It should also be noted that drugs must be taken continuously and without interruption, so that the virus is always suppressed and there is no possibility of mutation. If treatment is stopped, the virus is more likely to return to high levels. This is something that can be verified from the model. As a further simplification of the above model, two inputs can be combined into one unit, which operates in the third differential equation. In particular, after clinical studies, it was shown that the effects of RTI and PI drugs could not be isolated. In addition, combination therapy appears to be much more effective in parameter K than β. Based on these observations, the following nonlinear model is formed:

$$\dot{T}(t) = s - dT(t) - \beta T(t)v(t)$$

$$\dot{T}^*(t) = \beta T(t)v(t) - m_2 T^*(t)$$

$$\dot{v}(t) = \big(1 - u(t)\big)kT^*(t) - m_1 v(t)$$

The parameter u (t) indicates the effectiveness of combination therapy.

The point x $*$ ∈ Rn is an equilibrium point for the system x ˙ = f (t, x) if f (x $*$) = 0 for all t ≥ 0. Therefore, to determine the equilibrium points (2.1), we solve the system of equations we do

$$0 = s - dT(t) - \beta T(t)v(t)$$

$$0 = \beta T(t)v(t) - m_2 T^*(t)$$

$$0 = kT^*(t) - m_1 v(t)$$

In cases where T $*$ = v = 0, is the equilibrium

$$\left(\frac{s}{d} \quad 0 \quad 0\right)$$

And in cases where v = 0 is equilibrium

$$\left(\frac{m_1 m_2}{k\beta} \qquad \frac{s}{m_2} - \frac{dm_1}{k\beta} \qquad \frac{ks}{m_1 m_2} - \frac{d}{\beta}\right) = (240 \quad 21.6667 \quad 902.778)$$

Adele first belongs to a healthy, non-infected person, so it is not considered. The second equilibrium corresponds to the equilibrium point after patients enter the clinical delay stage. To linearize the system around equilibrium, we first calculate the Jacobian system, which by

$$J(f) = \begin{pmatrix} -d - \beta v & 0 & -\beta T \\ \beta v & -m_2 & \beta T \\ 0 & k & -m_1 \end{pmatrix}$$

By calculating the Jacobian eigenvalues, we find that they are all stable, and therefore the equilibrium point is hyperbolic. This, in combination with Hartman Grobman theorem, ensures that linearity is possible, and the linearized system maintains the qualitative properties of the nonlinear system around equilibrium. Defined by adding inputs

$$\tilde{f}_1(T, T^*, v, u_1, u_2) = s - dT(t) - \big(1 - u_1(t)\big)\beta T(t)v(t)$$

$$\tilde{f}_2(T, T^*, v, u_1, u_2) = \big(1 - u_1(t)\big)\beta T(t)v(t) - m_2 T^*(t)$$

$$\tilde{f}_3(T, T^*, v, u_1, u_2) = \big(1 - u_2(t)\big)kT^*(t) - m_1 v(t)$$

The linear system is as follows:

$$\begin{pmatrix} \dot{T} \\ \dot{T^*} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} \frac{\partial \tilde{f}_1}{\partial T} & \frac{\partial \tilde{f}_1}{\partial T^*} & \frac{\partial \tilde{f}_1}{\partial v} \\ \frac{\partial \tilde{f}_2}{\partial T} & \frac{\partial \tilde{f}_2}{\partial T^*} & \frac{\partial \tilde{f}_2}{\partial v} \\ \frac{\partial \tilde{f}_3}{\partial T} & \frac{\partial \tilde{f}_3}{\partial T^*} & \frac{\partial \tilde{f}_3}{\partial v} \end{pmatrix} \begin{pmatrix} T \\ T^* \\ v \end{pmatrix} + \begin{pmatrix} \frac{\partial \tilde{f}_1}{\partial u_1} & \frac{\partial \tilde{f}_1}{\partial u_2} \\ \frac{\partial \tilde{f}_2}{\partial u_1} & \frac{\partial \tilde{f}_2}{\partial u_2} \\ \frac{\partial \tilde{f}_3}{\partial u_1} & \frac{\partial \tilde{f}_3}{\partial u_2} \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}$$

Calculate the values of the above matrices for

$$(T \quad T^* \quad v \quad u_1 \quad u_2) = (240 \quad 21.6667 \quad 902.778 \quad 0 \quad 0)$$

Ends the system of government space

$$\begin{pmatrix} \dot{T} \\ \dot{T^*} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} -0.0417 & 0 & -0.0058 \\ 0.0217 & -0.24 & 0.0058 \\ 0 & 100 & -2.4 \end{pmatrix} \begin{pmatrix} T \\ T^* \\ v \end{pmatrix} + \begin{pmatrix} 5.2 & 0 \\ -5.2 & 0 \\ 0 & -2166.67 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}$$

$$y = (0 \quad 0 \quad 1) \begin{pmatrix} T \\ T^* \\ v \end{pmatrix}$$

Where a viral load output is selected. The next step in system space analysis is to calculate its transmission performance, which gives the relationship between the output and each input. it will be counted:

$$G(s) = C(sI_3 - A)^{-1}B$$
$$= \left(\frac{-520s - 10.4}{s^3 + 2.682s^2 + 0.1061s + 0.01242} \quad \frac{-2167s^2 - 610.4s - 21.68}{s^3 + 2.682s^2 + 0.1061s + 0.01242} \right)$$

The controllability matrix is given by

$$\mathcal{L} = (B \quad AB \quad A^2B) = \begin{pmatrix} 5.2 & 0 & -0.216667 & 12.48 & 3.00423 & -30.472 \\ -5.2 & 0 & 1.36067 & -12.48 & -3.32645 & 33.2176 \\ 0 & -2166.67 & -520 & 5200 & 1384.07 & -13728 \end{pmatrix}$$

And it has a full rating and so the system is controllable. Therefore, the system can be compensated by using open or closed loop controllers. If a single nonlinear input system is considered, as presented in the previous section, it follows the same procedure to the state space system, where the new matrix B of consists of only the second column B. Although the linear model is a simplification and only records its dynamic properties during equilibrium, it can be used as a basis for illustrating a set of control system engineering problems.

Result

The time series of healthy CD4 + cells, infected CD4 + and free viruses are plotted for simple dynamic equations.

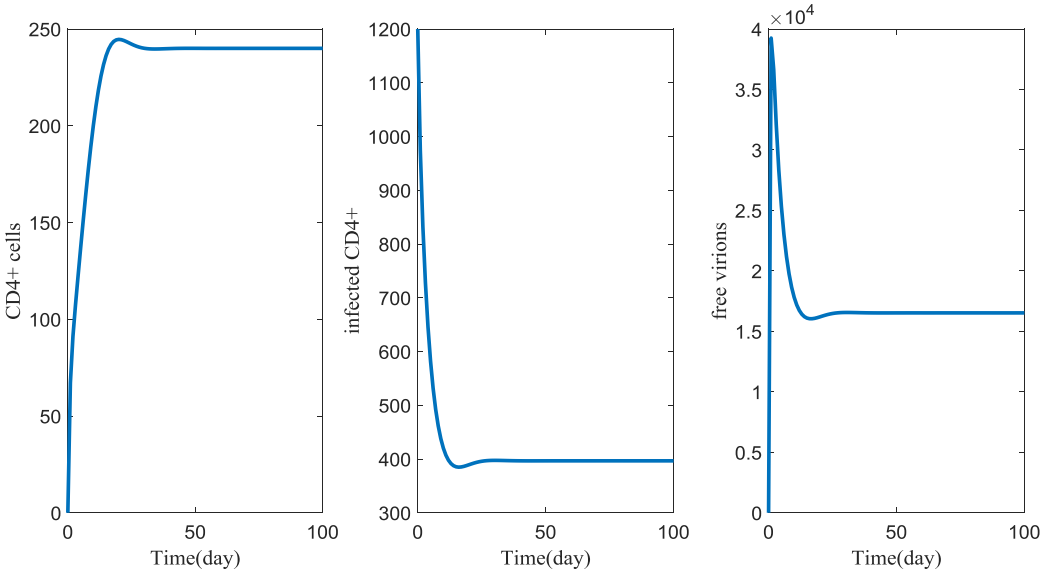

Figure. Disease progression.

Drug categories such as non-nucleoside reverse transcriptase inhibitors (NNRTIs), reverse nucleoside transcriptase inhibitors (NRTIs), and fusion / entry inhibitors. Because most current bibliographies focus on RTIs and PIs, we adopt this line of analysis. RTIs work by blocking infection of new T cells, while PIs prevent the production of new viruses. Here, by trying different combinations of the two drugs, their effect on viral load can be observed, as shown in the figure below. In fact, it can be seen that the viral load is successfully suppressed.

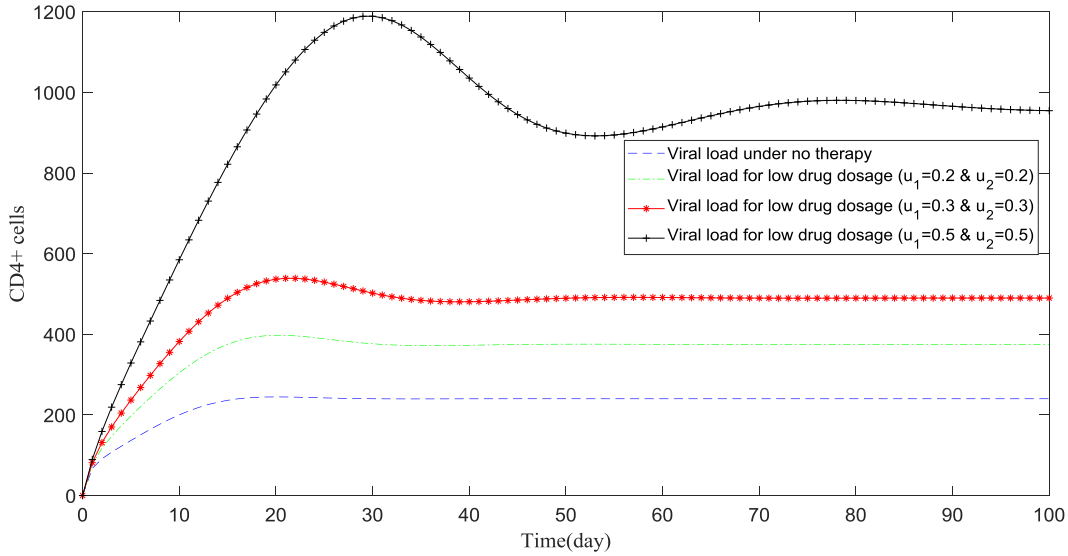

Figure. Viral load for different drug dosages.

The parameter u (t) indicates the effectiveness of combination therapy. The response of the systems for a single input model is shown in the figure below. The significant difference that we observe, although we observe in relation to the two input models, is that the viral load shows different and larger drugs after discontinuation of different drugs.

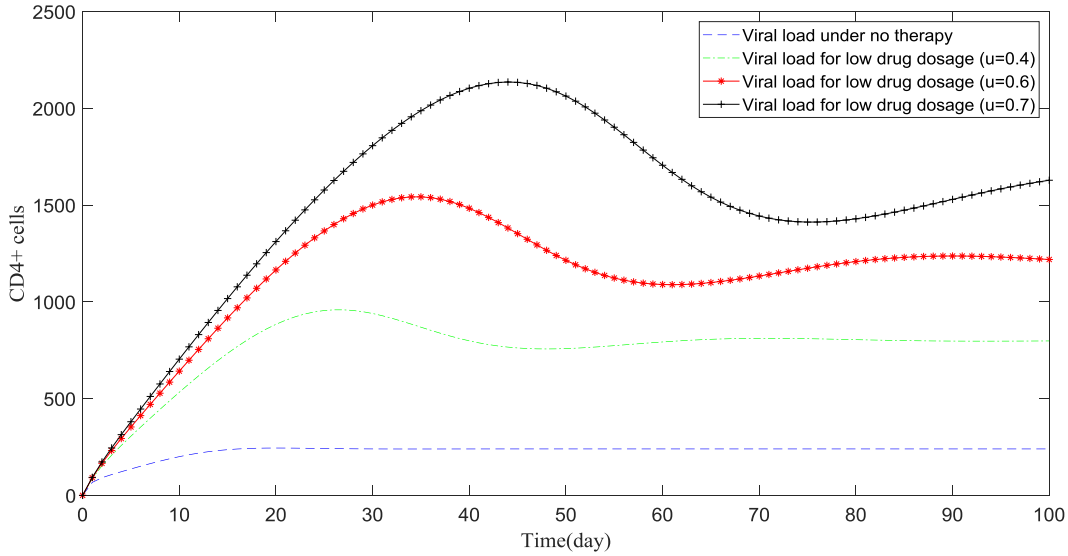

Figure. Viral load for the single input system.

Conclusion

This paper presents a basic nonlinear model that describes HIV infection. The effect of antiviral therapy under the influence of variable drug was evaluated. Then a Linra mode space model was developed to simplify the dynamic behavior of the system and various control engineering problems in which it is proposed to compensate for it like the design of controllers. Each part of this work could potentially be included in the curriculum of linear and nonlinear dynamic systems and could be combined using computer software such as Matlab to simulate the above models. This modeling was done using ode in Matlab.

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