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A DYNAMIC MODEL FOR HIV INFECTION

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Abstract. A dynamical model that describes the effect of the HIV virus on the immune system is presented. The effect of introducing antiretroviral therapy on the model, consisting of RTIs and PIs, is investigated, along with the result of undesired treatment interruption. The effect of both drugs can be combined into a single input that further simplifies the model. Furthermore, the system is linearized around the equilibrium, leading to a system of linear differential equations of first order that can be integrated into courses of control systems engineering in higher education.

1. Introduction

According to the most recent HIV/AIDS surveillance report in Greece, on October of 2015 [7], the Hellenic Center For Disease Control & Prevention (H.C.D.C.P.) has so far reported 15.109 positive HIV infections. Of these, 3.782 have already developed AIDS and around 7.700 are subject to antiretroviral therapy (ART). The number of deaths resulting from the infection amounts to 2.562. According to the H.C.D.C.P. 2014 report [8], the largest portion of HIV cases has been diagnosed in men who had sex with men (46.2%), followed by the categories of heterosexual sexual contact (21.3%) and injecting drug users (10.8%).

More specifically, during the period of 2011-2013, there was a big rise in the number of cases in injecting drug users, that was followed by a steady decrease during the last two years. Yet, as the Office for HIV and Sexually Transmitted Diseases emphasizes, although the last data on the decrease infections are positive, they should not be considered comforting. There must be constant actions for the awareness of both the high risk groups and the general population.

Motivated by similar and even more alarming statistics in South Africa, the University of Pretoria, being aware of the fact that the student population generally falls into the high risk groups, mainly due to lack of awareness, decided to organise an action to inform the students about the problem. The department of Electrical, Electronic and Computer Engineering, the department of Telematic Learning and Education Innovation and the Center for the Study of AIDS came together and developed a CD [4, 5], with the aim of presenting a model for the HIV infection from a control theory perspective. Their aim was to present the problem through

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a mathematical model that would introduce the students to the field of control systems engineering, motivating them at the same time to learn more about this sensitive subject.

Base on this innovative idea by the University of Pretoria, we propose an analytical description of the dynamic model for HIV infection, with the purpose of fulfilling two different objectives. First, to present a detailed control engineering problem that can be implemented in a vast variety of undergraduate courses in the field of dynamical systems, thus making the syllabus much more interesting through the perspective of real life applications. This study, as will be shown later, is subject to extensive research [1–3, 6, 9, 10, 12–15, 18–22, 24, 25] and can be extended to master and doctoral studies. Secondly, the awareness abong students on the subject should be a natural consequence of taking such a subject.

2. The dynamical model of HIV

The Human Immunodeficiency Virus (HIV) acts by attacking the immune system, causing its progressive failure over time and its collapse after years (when no treatment is administered). The virus can be transmitted mainly through sexual intercourse without protection. In addition the virus can be spread through sharing needles in drug users and in health care accidents, through blood, organ or sperm donations and from mother to child during pregnancy or birth [6].

The virus acts by infecting the CD4+ T cells. In the initial days of the infection, the virus rapidly multiplies and as a result in the first 2-12 weeks the patient develops general flu-like symptoms like fever, chills, rashes, night sweats, sore throat, fatigue and swollen lymph nodes. This is called the *acute HIV infection stage*. The spread of the virus activates the immune system to fight of the infection. This leads after a period of 12-15 weeks to the suppression of the virus spread and the stabilization of the immune system.

Now, the patient enters the *clinical latency stage*, also called the *chronic HIV infection*. During this stage there is a balance between healthy CD4+ cells and viral load, so the virus is still active but is repressed by the immune system and reproduces at very low levels. This stage may last as long as 10 years for patients who do not take medication and up to many decades for patients who are properly administered to antiretroviral therapy. Eventually, through the chronic deterioration, the immune system becomes weak and vulnerable, making the individual vulnerable to opportunistic infections. This is the final stage of the HIV infections and is called the Acquired ImmunoDeficiency Syndrome (AIDS). It should be noted though that not all HIV positive people advance to this stage.

A simple model that describes the effect of the HIV to the immune system can be constructed by describing the interactions between healthy CD4+ T cells, infected CD4+ cells and the viral load, see Figure 1. Healthy CD4+ cells are produced by the thymus at a constant rate of s and die at a rate d. They are infected by the virus at a rate that is proportional to the product of their number and the viral load. The effectiveness of the infection is given by a constant β. The infected CD4+ cells result from the infection of healthy cells and die at a constant rate m_2. Free virus particles, known as virions are produced from infected CD4+ cells at a rate k and die at a rate m_1 [2, 4, 5, 14, 15].

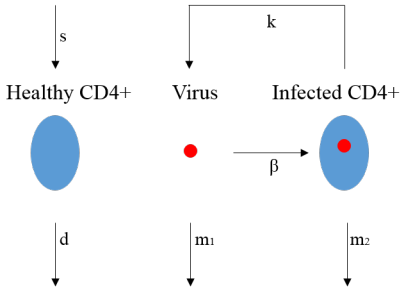

FIGURE 1. Interaction of HIV and CD4+ cells.

These interactions between healthy CD4+ cells, infected CD4+ and free virions can be described by the following system of nonlinear equations

$$\dot{T}(t) = s - dT(t) - \beta T(t)v(t) \tag{2.1a}$$
$$\dot{T}^*(t) = \beta T(t)v(t) - m_2 T^*(t) \tag{2.1b}$$
$$\dot{v}(t) = kT^*(t) - m_1 v(t) \tag{2.1c}$$

where $T(t)$ the number of healthy CD4+, $T^*(t)$ the number of infected CD4+ and $v(t)$ the number of virions, also known as the viral load. Typical values for the parameters of the system are given in Table 1, according to [2, 4, 5].

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	10mm^{-3}/day
β	Infectivity rate of virions	$2.4\times10^{-5}\text{mm}^{-3}$/day
m_1	Death rate of virus	2.4/day
m_2	Death rate of infected T cells	0.24/day

TABLE 1. Typical values for the system parameters.

A typical progression for the disease is shown in Figure 2. It is clear that after initial infection, there is a rise in the infected CD4+ cells and after the reaction by the immune system,the system is stabilized and we have a pass to the clinical latency stage.

It should also be noted that the system always ends up in the same equilibrium point, regardless of initial condition of the patient. This can be seen in Figure 3, which shows multiple trajectories for varying initial conditions (note that some may correspond to unrealistic data).

3. Antiretroviral treatment

Highly active antiretroviral therapy, or HAART, consists of taking multiple drugs with different antiviral targets that maintain the function of the immune system and suppress the virus. Two basic categories of antiretroviral drugs are the reverse transcriptase inhibitors or RTIs and protease inhibitors or PIs. There are also other

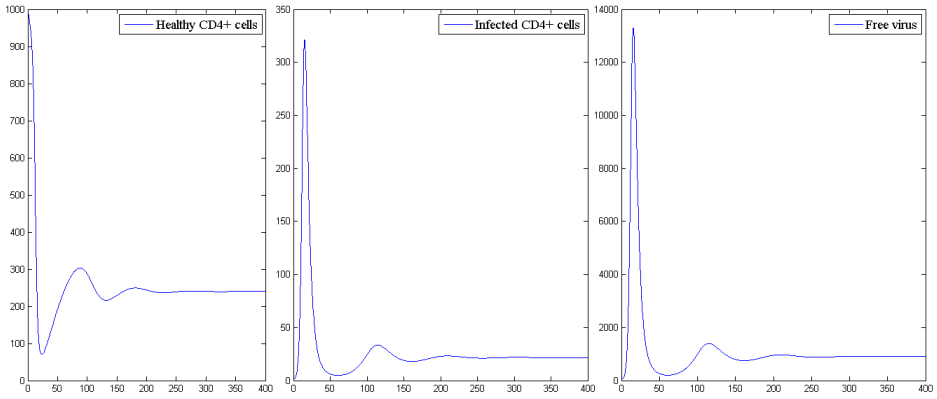

FIGURE 2. Disease progression.

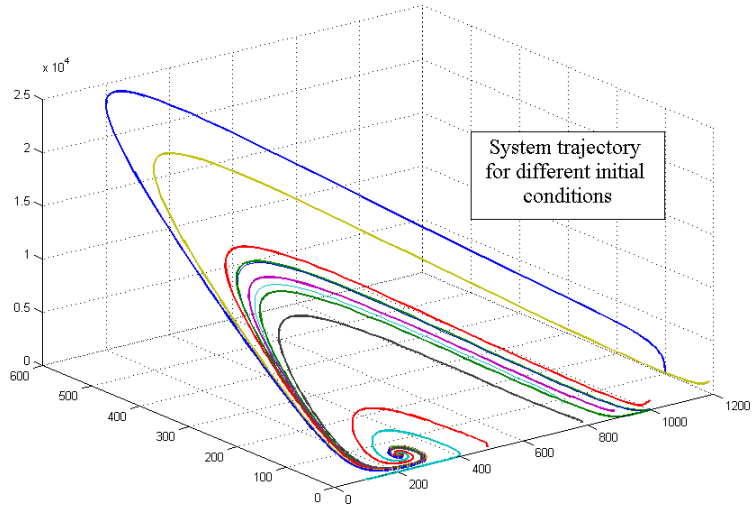

FIGURE 3. System trajectories for different initial conditions.

drug categories like non-nucleoside reverse-transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs) and fusion/entry inhibitors. Since though most of the current bibliography focuses on RTIs and PIs, we adopt this line of analysis. RTIs act by blocking the infection of new T cells while PIs prevent the production of new virions. Taking into consideration the effect of these artiretroviral drugs, model (2.1) takes the form [2, 4, 5, 14, 15]:

$$\dot{T}(t) = s - dT(t) - (1 - u_1(t))\,\beta T(t)v(t) \tag{3.1a}$$

$$\dot{T}^*(t) = (1 - u_1(t))\,\beta T(t)v(t) - m_2 T^*(t) \tag{3.1b}$$

$$\dot{v}(t) = (1 - u_2(t))\,kT^*(t) - m_1 v(t) \tag{3.1c}$$

where the terms $(1-u_1(t))$ and $(1-u_2(t))$ represent the effectiveness of RTIs and PIs respectively (for $u_{1,2}=0$ the drug is not administered, while for $u_{1,2}=1$ the treatment is 100% effective, which of course is not achievable). Here, by trying different combinations of intensity for the two drugs we can observe their effect on the viral load, as shown in Figure 4. Indeed, it can be seen that the viral load is successfully suppressed. The treatment is initiated at the 150th day.

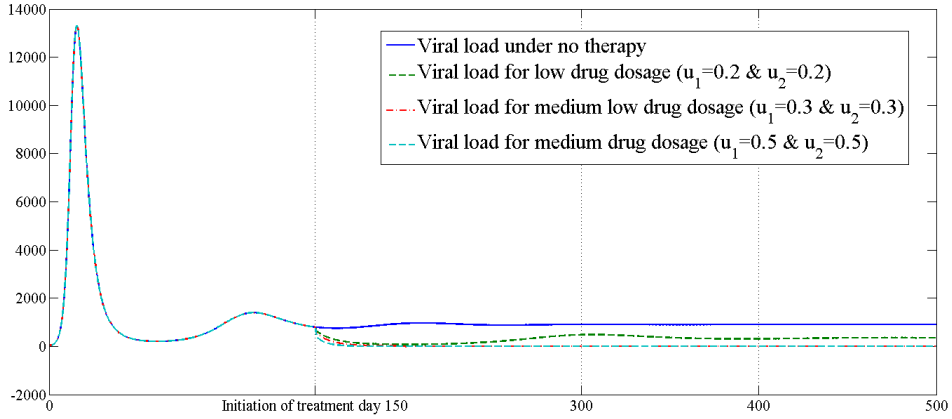

FIGURE 4. Viral load for different drug dosages.

What should also be noted is that the drugs should be taken continuously and with no interruptions, so that the virus is always suppressed and is not given the chance to mutate. In case the treatment is interrupted, there is a big possibility that the virus will regress back to high levels. This is something that can be confirmed from the model (3.1). Indeed, as can be seen in Figure 5, if the treatment starts at day 150 but is terminated at day 400, the virus load may stay low for a maximum of 150 more days, depending on the effectiveness of the drugs, but rises back up afterwards. The issue of treatment interruption has been clinically studied in [24].

As a further simplification of the model (3.1), the two inputs can be combined into a single one, that acts on the third differential equation. More specifically in [2,14,15], it was shown after clinical studies that the effects of RTI and PI drugs cannot be considered decoupled. Furthermore, the combined treatment seems to be much more effective on the parameter k than in β. Taking into account these observations, the nonlinear model (3.1) takes the form

$$\dot{T}(t) = s - dT(t) - \beta T(t)v(t) \tag{3.2a}$$

$$\dot{T}^*(t) = \beta T(t)v(t) - m_2 T^*(t) \tag{3.2b}$$

$$\dot{v}(t) = (1-u(t))\, kT^*(t) - m_1 v(t) \tag{3.2c}$$

where the parameter $u(t)$ denotes the effectiveness of the combined treatment. The systems response for a single input model is shown in Figure 6. A notable difference that we observe though in constrast to the two input model (3.1) is that the viral load exhibits different and larger overshoot for different drug dosages, after the interruption of treatment.

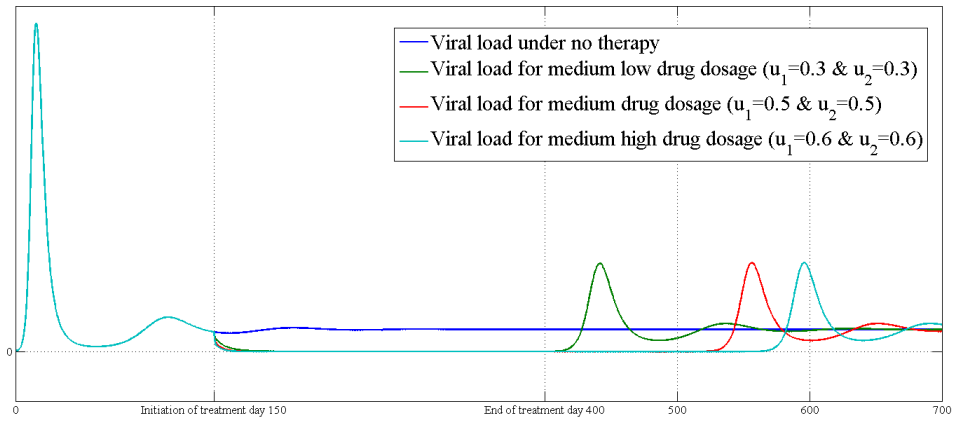

FIGURE 5. Viral load after treatment interruption.

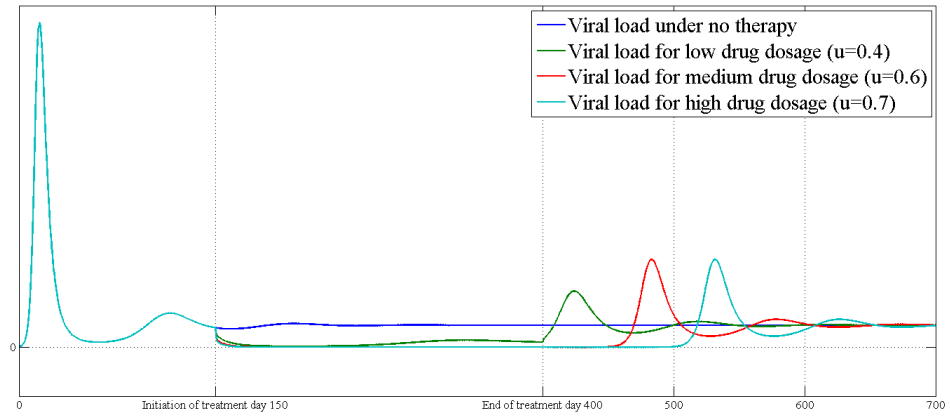

FIGURE 6. Viral load for the single input system.

4. LINEARIZATION

The analysis of the nonlinear systems (2.1),(3.1),(3.2) is a very complex and challenging task. For this reason, our aim is to determine the dynamical behavior of the system around its equilibrium points.

Definition 4.1. *[23] A point $x^* \in \mathbb{R}^n$ is an equilibrium point for the system $\dot{x} = f(t,x)$ if $f(x^*) = 0$ for all $t \geq 0$.*

So, in order to specify the equilibrium points of (2.1), we solve the system of equations

$$0 = s - dT(t) - \beta T(t)v(t) \tag{4.1a}$$

$$0 = \beta T(t)v(t) - m_2 T^*(t) \tag{4.1b}$$

$$0 = kT^*(t) - m_1 v(t) \tag{4.1c}$$

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

$$\begin{pmatrix} \frac{s}{d} & 0 & 0 \end{pmatrix} \tag{4.2}$$

and in case where $v \neq 0$ the equilibrium is

$$\begin{pmatrix} \frac{m_1 m_2}{k\beta} & \frac{s}{m_2} - \frac{dm_1}{\beta k} & \frac{ks}{m_1 m_2} - \frac{d}{\beta} \end{pmatrix} = \begin{pmatrix} 240 & 21.6667 & 902.778 \end{pmatrix} \tag{4.3}$$

The first equilibrium corresponds to a healthy uninfected individual, so it is not of interest. The second equilibrium corresponds to the equilibrium point after the patients enters the clinical latency stage. To linearise the system around the equilibrium, we first compute the Jacobian of the system, which is given by

$$J(f) = \begin{pmatrix} -d - \beta v & 0 & -\beta T \\ \beta v & -m_2 & \beta T \\ 0 & k & -m_1 \end{pmatrix} \tag{4.4}$$

Computing the eigenvalues of the Jacobian, we find that they are all stable, and thus the equilibrium point is hyperbolic [11]. This, in combination with the Hartman-Grobman theorem [23] guarantees that the linearization is possible and that the linearized system preserves the qualitative properties of the nonlinear system around the equilibrium. With the addition of inputs, we define

$$\tilde{f}_1(T, T^*, v, u_1, u_2) = s - dT(t) - (1 - u_1)\beta T(t)v(t) \tag{4.5a}$$
$$\tilde{f}_2(T, T^*, v, u_1, u_2) = (1 - u_1)\beta T(t)v(t) - m_2 T^*(t) \tag{4.5b}$$
$$\tilde{f}_3(T, T^*, v, u_1, u_2) = (1 - u_2)kT^*(t) - m_1 v(t) \tag{4.5c}$$

The linearized system is [11]:

$$\begin{pmatrix} \dot{T} \\ \dot{T}^* \\ \dot{v} \end{pmatrix} = \begin{pmatrix} \frac{\partial \tilde{f}_1}{\partial T} & \frac{\partial \tilde{f}_1}{\partial T^*} & \frac{\partial \tilde{f}_1}{\partial v} \\ \frac{\partial \tilde{f}_2}{\partial T} & \frac{\partial \tilde{f}_2}{\partial T^*} & \frac{\partial \tilde{f}_2}{\partial v} \\ \frac{\partial \tilde{f}_3}{\partial T} & \frac{\partial \tilde{f}_3}{\partial T^*} & \frac{\partial \tilde{f}_3}{\partial v} \end{pmatrix} \begin{pmatrix} T \\ T^* \\ v \end{pmatrix} + \begin{pmatrix} \frac{\partial \tilde{f}_1}{\partial u_1} & \frac{\partial \tilde{f}_1}{\partial u_2} \\ \frac{\partial \tilde{f}_2}{\partial u_1} & \frac{\partial \tilde{f}_2}{\partial u_2} \\ \frac{\partial \tilde{f}_3}{\partial u_1} & \frac{\partial \tilde{f}_3}{\partial u_2} \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \tag{4.6}$$

computing the values of the above matrices for

$$\begin{pmatrix} T & T^* & v & u_1 & u_2 \end{pmatrix} = \begin{pmatrix} 240 & 21.6667 & 902.778 & 0 & 0 \end{pmatrix} \tag{4.7}$$

we end up with the state space system

$$\begin{pmatrix} \dot{T} \\ \dot{T}^* \\ \dot{v} \end{pmatrix} = \underbrace{\begin{pmatrix} -0.0417 & 0 & -0.0058 \\ 0.0217 & -0.24 & 0.0058 \\ 0 & 100 & -2.4 \end{pmatrix}}_{A} \begin{pmatrix} T \\ T^* \\ v \end{pmatrix} + \underbrace{\begin{pmatrix} 5.2 & 0 \\ -5.2 & 0 \\ 0 & -2166.67 \end{pmatrix}}_{B} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \tag{4.8a}$$

$$y = \underbrace{\begin{pmatrix} 0 & 0 & 1 \end{pmatrix}}_{C} \begin{pmatrix} T \\ T^* \\ v \end{pmatrix} \tag{4.8b}$$

where we chose as an output the viral load. The next step in the analysis of the state space system (4.8) is to compute its transfer function, that gives the connection between the output and each input [16]. It is computed as

$$G(s) = C(sI_3 - A)^{-1}B = \tag{4.9}$$
$$= \begin{pmatrix} \frac{-520s - 10.4}{s^3 + 2.682s^2 + 0.1061s + 0.01242} & \frac{-2167s^2 - 610.4s - 21.68}{s^3 + 2.682s^2 + 0.1061s + 0.01242} \end{pmatrix} \tag{4.10}$$

The controllability matrix is given by

$$\mathcal{L} = \begin{pmatrix} B & AB & A^2B \end{pmatrix} = \tag{4.11}$$

$$= \begin{pmatrix} 5.2 & 0 & -0.216667 & 12.48 & 3.00423 & -30.472 \\ -5.2 & 0 & 1.36067 & -12.48 & -3.32645 & 33.2176 \\ 0 & -2166.67 & -520. & 5200. & 1384.07 & -13728. \end{pmatrix} \tag{4.12}$$

and it has full rank and so the system is controllable. Thus, the system can be compensated through the use of open or closed loop controllers.

If we consider the single input nonlinear system (3.2), as presented in the previous section, then following the same procedure we end up in the state space system (4.8), where the new matrix $\bar{B}$ consists of just the second column of B.

Although the linear model (4.8) is a simplification of (2.1) and only captures its dynamical qualities around the equilibrium, can be used as a basis for the demonstration of a plethora of problems of control systems engineering. Such topics include the state feedback of the system (4.8) and the computation of its gain margin, the design of PID controllers for the reduction of the viral load, the evaluation of the sampling time through Bode diagrams to decide the frequency in which the patient should be tested and many more.

5. Conclusions

We presented a fundamental nonlinear model that describes the HIV infection. The effect of antiretroviral treatment was studied under variable drug effectiveness. Then a linera state space model was developed to further simplify the dynamic behavior of the system and various control engineering problems where proposed like the design of controllers for its compensation. Every part of this work can be potentially integrated into the syllabus of linear and nonlinear dynamical systems courses and can be combined with the use of computer software like Matlab [16, 17] to simulate the above models. Further research on the field of HIV/AIDS infection constitutes the study of more complex nonlinear models [1, 3, 9, 12, 19, 25] that describe more accurately the complicated nature of the virus, the problem of feedback linearization of the nonlinear system [2, 14, 15, 20] and the use of time variant or even impulsive inputs for its control [2, 14, 15, 21].

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