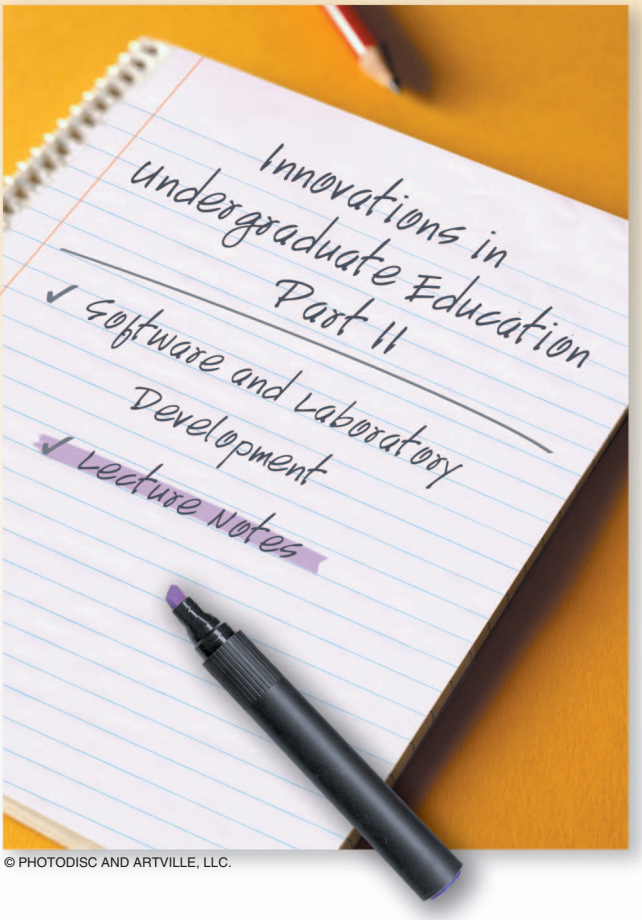
FEATURE

Can HIV/AIDS Be Controlled?

Applying control engineering concepts outside traditional fields



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By Ian Craig and Xiaohua Xia

There is currently no cure for the acquired immune deficiency syndrome (AIDS). Medication can suppress the human immunodeficiency virus (HIV), as described in this article, but can never eradicate it completely. High levels of HIV occur in most cases during all stages of infection, and it is estimated that as many as 10^{10} viruses are produced and destroyed in an infected individual each day [1]. HIV/AIDS is therefore a deadly serious and incurable disease—the title of this article should not create the impression that it is not. In fact, AIDS can cause tremendous suffering, leading often to death by complications.

Estimates for 2002 show that 4.69 million South Africans are infected with HIV, and that by the year 2008, half a million South Africans will die every year from AIDS-related causes [2]. Given this dire situation, and the realization that students generally fall into a high-risk group, the University of Pretoria, the largest residential university in South Africa, has launched several initiatives to promote the understanding of the disease among its student population. Recent initiatives include the development of an HIV/AIDS educational CD [3],[4], and the use of an HIV/AIDS model in an introductory control course to illustrate standard control systems material. The CD, which contains various HIV/AIDS models [5] packaged as Java Applets, complements the text [6] that is prescribed for this course.

HIV/AIDS Mathematical Model

The simplest HIV/AIDS mathematical model can best be understood through the interactions of healthy CD4+ cells (T), infected CD4+ cells (T^*), and free viruses (v),

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modeled by

$$\begin{aligned}\frac{dT}{dt} &= s - dT - \beta Tv,\\ \frac{dT^*}{dt} &= \beta Tv - \mu T^*,\\ \frac{dv}{dt} &= kT^* - cv,\end{aligned} \tag{1}$$

which are described in Figure 1 [5]. HIV largely exerts its effect on the immune system by destroying CD4+ T cells that are critical in helping the body fight infections. Free virus refers to the HIV particles found in the blood plasma. Model parameters, their typical values, and a sample disease progression can be found in [3].

HIV/AIDS Model Analysis for Control

The system (1) has two equilibrium points [3], one of which is

$$\left(\frac{c\mu}{\beta k}, \frac{s}{\mu} - \frac{dc}{\beta k}, \frac{ks}{c\mu} - \frac{d}{\beta}\right). \tag{2}$$

Using Lyapunov analysis [7], it can be shown that while the virus spreads after infection, the abundance of uninfected cells, infected cells, and free viruses settles at the locally asymptotically stable equilibrium given in (2).

Two major categories of antiretroviral drugs can be accommodated in (1), namely, reverse transcriptase inhibitors (RTIs), as shown in Figure 2, and protease inhibitors (PIs). The parameter β can be taken as the RTI control variable [8], and, similarly, the effect of PIs is lumped into the parameter k in model (1). This equation can now be rewritten to accommodate control actions or chemotherapy treatment in the form

$$\begin{aligned}\frac{dT}{dt} &= s - dT - (1-u_1)\beta Tv,\\ \frac{dT^*}{dt} &= (1-u_1)\beta Tv - \mu T^*,\\ \frac{dv}{dt} &= (1-u_2)\, kT^* - cv,\end{aligned} \tag{3}$$

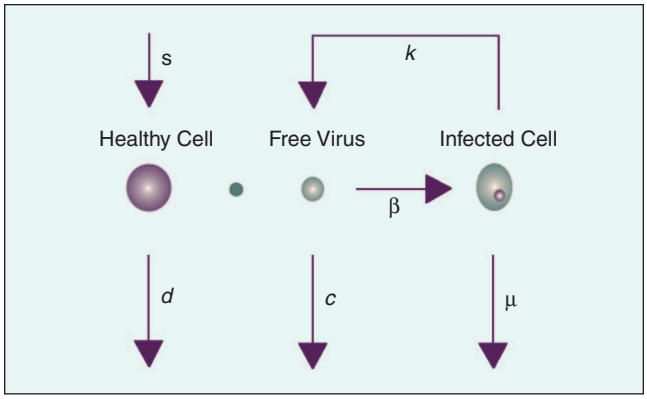

Figure 1. *Schematic illustration of the basic HIV model [4]. The healthy CD4+ cells are produced from a source, such as the thymus, at a constant rate s, and die at a rate d. The cells are infected by the virus at a rate that is proportional to the product of their abundance and the amount of free virus particles. The proportionality constant β is an indication of the effectiveness of the infection process. The infected CD4+ cells result from the infection of healthy CD4+ cells and die at a rate μ. Free virus particles are produced from infected CD4+ cells at a rate k and are cleared at a rate c.*

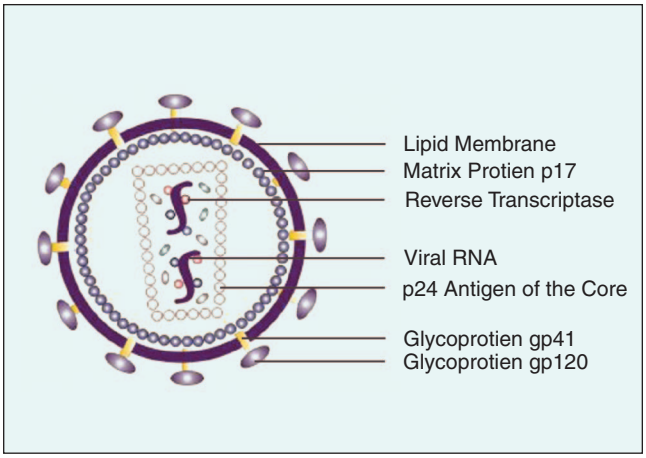

Figure 2. *Structure of HIV [4]. An enzyme that is a part of the HIV nucleocapsid, called the reverse transcriptase, transcribes the viral RNA that has entered the host (CD4+) cell as complementary DNA sequences. This transcription process is blocked by antiretroviral drugs called reverse transcriptase inhibitors. Without reverse transcriptase, the viral genome cannot be incorporated into the lymphocyte host cell DNA, and HIV replication cannot occur.*

in which u_1 and u_2 represent the efficacy of the two types of drugs, where a single application of an RTI corresponds to making $u_2 = 0$, and where u_1 satisfies $0 \le u_1 \le 1$.

Student Project

Model (3) is highly nonlinear and has two inputs, which generally make it ill-suited for use in a typical introductory control systems course where the focus is on the analysis and design of controllers for linear time-invariant and single-input, single-output systems. However, by using only one control input with RTI as the antiretroviral agent along with one controlled output (v), and deriving a linear approximation of (3), students can obtain valuable qualitative and quantitative insights into the interactions between HIV and the immune system. In practice, multiple drug types comprising more than one control action are used together as in highly active antiretroviral therapy (HAART) [9].

The project task is therefore to linearize (3) around the operating point (2), to analyze the resulting model, to design a controller to reduce the viral load by 90% in eight weeks from the time treatment is initiated, and to continue to suppress the viral load to below 50 copies per milliliter of plasma after six months as recommended in U.S. HIV/AIDS treatment guidelines [10].

Results

Linearizing at the operating point (T_0, T_0^*, v_0) (with $u_{10} = 0$) results in the state transition matrix A and input matrix B given by

$$A = \begin{bmatrix} -d - \beta v_0 & 0 & -\beta T_0 \\ \beta v_0 & -\mu & \beta T_0 \\ 0 & k & -c \end{bmatrix}, \quad B = \begin{bmatrix} \beta T_0 v_0 \\ -\beta T_0 v_0 \\ 0 \end{bmatrix}. \quad (4)$$

With the typical parameter values given in [3], the operating point (2) has the numerical value (240.00, 21.67, 902.78). Furthermore, the corresponding pair (A, B) is given by

$$A_1 = \begin{bmatrix} -0.0417 & 0 & -0.0058 \\ 0.0217 & -0.24 & 0.0058 \\ 0 & 100 & -2.4 \end{bmatrix}, \; B_1 = \begin{bmatrix} 5.2 \\ -5.2 \\ 0 \end{bmatrix}. \quad (5)$$

The eigenvalues of A_1 in (5) are $(-0.0199 + 0.6658\text{i}; -0.0199 - 0.6658\text{i}; -2.6418)$, and thus the system is asymptotically stable at the operating point (2).

A state-feedback controller can be designed to meet the required specifications. The pair (A_1, B_1) is completely controllable, and all of the states are assumed measurable. The resulting gain is

$$K = [-3.6730\text{e}{-003} \quad -2.0957\text{e}{+000} \quad 4.9262\text{e}{-002}]. \quad (6)$$

In reality, health workers close the loop by administering anti-retroviral drugs based on measurements of T and v. Measurements of T^* are usually not readily available but can be deduced from other measurements by using an observer. See [11] for a more detailed analysis.

The uncontrolled response and the closed-loop step response are shown in Figure 3. The figure shows that the controller meets the recommended treatment guidelines [10]. Although the linear model (5) is valid only around operating point (2), controller (6) gives adequate results when applied to the nonlinear model (3).

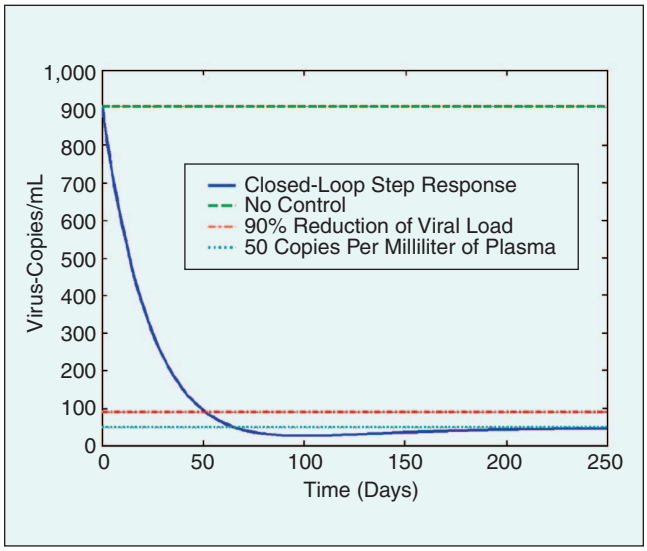

Figure 3. *HI viral response. When no control is taken, the free viruses remain at the equilibrium value 902.78. The controller is able to reduce the viral load by 90% in about 51 days (less than eight weeks) and continues to suppress it to below 50 copies per milliliter of plasma after about 66 days.*

Conclusions

Can HIV/AIDS be controlled? Yes, in the sense that medication can suppress HIV as indicated. This suppression, however, does not constitute a cure for the disease, as HIV *cannot* be eradicated by currently available medication. Once you have HIV, the virus remains in your body for life!

In the project described here students are given some idea of how HIV treatment strategies can be developed to contain HIV. Students benefit not only from the topical nature of the subject but also from an improved understanding of how control engineering concepts can be applied outside of traditional application fields.

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Unnecessary Thinking

There are some who feel that the mechanization of industry and automatic control will lead to a stagnation of human intelligence and enterprise by making it unnecessary for men even to think about problems. Actually, history shows that the significant advances in technology and science have often accompanied improvements in justice and expressions of beauty which are more apt to occur when men have leisure and material comfort and are not totally occupied with the business of keeping alive. The history of automatic control shows that it not only can produce things of finer quality in abundance, but it also can perform tasks that direct human control could not accomplish. In addition to furthering a reduction of working hours, automatic control, like mechanical power, has eliminated much drudgery. As a consequence many workers are now being trained to be the masters of their machines. This raising of the status of the worker contributes to the general welfare.

— *Quoted from R. S. Kirby et al,* Engineering in History, *reprinted by Dover Pub., 1990.*