A Novel Approach to Determine Dosage in Treatment of AIDS Based on Direct Self Tuning Regulator (STR) Theory and Linearization Around Equilibrium Condition

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Abstract

One of the main problems related to AIDS, is lack of control, lack of identification and early treatment of this disease. Today physicians more than anything, control the disease relying on their experience and knowledge and time-consuming and complex experiments, nevertheless, human errors are inevitable. In this study, a new approach for control (treatment) of AIDS based on patient entry drug is proposed. This paper investigated AIDS's dynamic model such that couple inputs (RTI1 and PI2) have been simplified by one input and finally by using linearization around operating point, the dynamic model linearized only with one input. Finally, by applying control signal to the disease by using direct adaptive control (STR 3), the disease can be controlled adaptively as the patient's condition is not worse and controlled. The proposed system by combining these methods waiting for dynamic attribute in terms of composition and interaction to high matching accuracy is able to reach small amounts and a substantial sum of squared errors SSE_4, mean absolute error and mean square error MAE_5 MSE_6. The present methods, despite on high precision, are time-consuming and expensive. By comparing this method and those methods, we will discover accuracy and efficiency of these methods.

Keywords: AIDS, diseases, Adaptive Control, Self Tuning Regulator.

1. Introduction

Treatment of human immunodeficiency virus (HIV) remains a major challenge. About three decades ago, HIV began to spread worldwide at an alarming rate. It is reported that in 2007, 33.2 million people were living with HIV/AIDS, 2.5 million people were newly infected and 2.1 million people died due to development of AIDS [1]. Significant progress has been made in the treatment of HIV infected patients, resulting in improved quality of life and greater longevity. Nowadays, thanks to advances in drugs development and their combination in ‘‘drug cocktails’’, most of the patients maintain undetectable viral load and safely high T-cell count for several years. Most of the currently available anti-HIV drugs fall into one of two categories: Reverse Transcriptase Inhibitors (RTIs) and Protease Inhibitors (PIs). From a system theoretic approach, these families of drugs represent independent ‘‘control inputs’’. On one hand,

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RT inhibitors prevent HIV RNA from being converted into DNA, thus blocking integration of the viral code into the target cell. On the other hand, protease inhibitors affect the viral assembly process in the final stage of the viral life cycle, preventing the proper cutting and structuring of the viral proteins before their release from the host cell. Highly Active Antiretroviral Therapy (HAART) is the most prevalent treatment strategy for HIV infected patient. It uses two or more drugs, typically one or more RTI and one PI. However, these drugs have a number of side effects on vital human functions. Thus, HIV treatment methods have drawn attention from the biomedical and control engineers societies and many control methods have been reported for HIV treatment. The dynamic multidrug therapy problem is modeled in ref. [3] as an optimal control model that maximizes the inhibition of HIV. In ref.[4], finite horizon open loop control tools are applied to an HIV chemotherapy model using an objective function based on a combination of maximizing T-cells count and minimizing the systemic cost of chemotherapy. Continuous-time feedback control used in refs. [2,5–8]suppresses the viral load to undetectable levels while in refs.[9,10]model predictive control is performed. In ref. [13] gradual reduction of drug dose is shown to boost the immune response. In refs. [11, 12] the possibility of a long term non progress or (LTNP) is demonstrated. The previous studies developed several new approaches in the control of the HIV infection. Although sophisticated, these control schemes are not yet ready to be applied in real-life monitoring of patients because they do not provide a discrete-time drug posology but rather a continuous-time optimal control stated in terms of abstract mathematical parameters hardly interpreted by clinicians. This paper includes basic pharmacokinetics (PK) and pharmaco dynamics (PD) principles in the design of nonlinear control laws to reduce the gap between purely theoretical control laws and real clinical drug dosing. Furthermore, the majority of existing studies consider the HIV dynamics as a system with two independent control inputs, each input being related to one of the two drug types i.e. RTIs and PIs. To the best of our knowledge, this assumption is not confronted to real clinical data. In Section2, the AIDS/HIV has been explained. In section 3 the third order basic model of the HIV dynamics is presented. Section 4 Problem of HIV model explained. Section 5 describes the identification technique used in the paper. In next sections, respectively, control Input, Linearization and Adaptive Controller has been explained, and finally simulation and result presented.

2. Aids

AIDS; or the human immunodeficiency virus, or HIV, is the virus that causes HIV infection. During HIV infection, the virus attacks and destroys the infection-fighting CD4 cells of the body's immune system. Loss of CD4 cells makes it difficult for the immune system to fight infections. Acquired immunodeficiency syndrome, or AIDS, is the most advanced stage of HIV infection. HIV is transmitted (spread) through the blood, semen, genital fluids, or breast milk of a person infected with HIV. Having unprotected sex or sharing drug injection equipment (such as needles and syringes) with a person infected with HIV are the most common ways HIV is transmitted. You can't get HIV by shaking hands, hugging, or closed mouth kissing with a person who is infected with HIV. And you can't get HIV from contact with objects such as toilet seats, doorknobs, dishes, or drinking glasses used by a person infected with HIV. Even though it takes many years for symptoms of HIV to develop, a person infected with HIV can spread the virus at any stage of HIV infection. Detecting HIV early after infection and starting treatment with anti-HIV medications before symptoms of HIV develop can help people with HIV live longer, healthier lives. Treatment can also reduce the risk of transmission of HIV. Antiretroviral therapy (ART) is the recommended treatment for HIV

infection. ART involves taking a combination (regimen) of three or more anti-HIV medications daily. ART prevents HIV from multiplying and destroying infection-fighting CD4 cells. This helps the body fight off life-threatening infections and cancer. ART can't cure HIV, but anti-HIV medications help people infected with HIV live longer, healthier lives. [14]

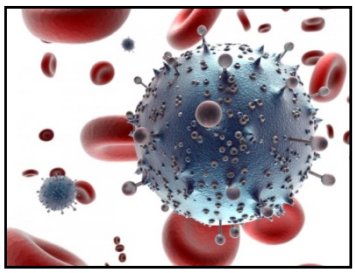


Fig. 1. AIDS Cell

3. Dynamical System

Model For the purposes of this investigation, we will ex-pound on the model of **Perelson** et al. [15]. The model in its original form will be given first, so that the more complicated version shown later may be seen as a very simple extension.

3.1. Dynamic Model

The target cells of HIV infection are lymphocyte helper cells, specially $CD4^+T$ cells. These cells become infected and begin to produce free virions. The main fact about HIV infection is reducing the count of $CD4^+T$ cells, which have an essential role in protecting body against different pathogens. So it is important to understand the dynamics of $CD4^+T$ cell count as a function of time. In HIV infection basic model, three groups of molecules are considered; Uninfected $CD4^+T$ cells (T), infected $CD4^+T$ cells (I) and viral load (V). Biological descriptions, translation to reactions and corresponding ODE's are presented in Table 1.

Table 1

HIV basic model Interaction

Biological description	Translation to reactions	Reaction rate	Translation to ODE
CD$+T cells production	0 → T	S	
CD4+T cell natural death	T → 0	D	
CD4+T cells become infected by virus	T+V → I+V	β	
Infected CD4+T cell death	I → 0	μ	
Virus replication infected CD4+T cells	I → I+V	k	
Virus natural death	V → 0	c	

Now, according to Table 1 and Section 2, the complete ODE model, which is sum of contributions from all reactions, is as follows:

$$\begin{aligned} \dot{x}_1 &= s - \delta x_1 - \beta x_1 x_3 \\ \dot{x}_2 &= \beta x_1 x_3 - \mu x_2 \\ \dot{x}_3 &= k x_2 - C x_3 \end{aligned} \tag{1}$$

4. Properties of HIV Model

There are two advantages to show the virus propagation in HIV disease, by the basic model (1).

1) From medical point of view, one important subject is the relative steady viral level during the asymptomatic stage of an HIV infection. This level is called "set-point". When body reaches this level, immune system develops HIV antibodies and begins to attempt to fight the virus. The higher the viral load of the set point, the faster the virus will progress to full blown AIDS (See [16]). It can be shown that set-point is the amount of V, in the equilibrium of virus depicted by the model (1) that is:

$$V^* = \frac{ks}{\mu c} - \frac{d}{\dot{\beta}} \tag{2}$$

2) It can be seen that a model of such a simple nature is able to adequately reflect the disease

progression from the initial infection to an asymptomatic stage after the set-point is reached (See [9az ICA 2010]).

5. Parameter Identification

According to identifiability theory presented in ref.[17], the 3D model (1) is algebraically identifiable from output measurements, namely the viral load (V) and the total CD4 count (T+T*) [18–20]. The identification of all the parameters of the 3D model from standard clinical data was first introduced in ref. [21].This approach was based on the nonlinear simplex optimization method. A new estimation method was introduced in ref.[22].It is based on a Monte-Carlo approach which is heuristic and relies also on the simplex optimization algorithm. This method enables having stable and robust results even for ill-conditioned problems as it is the case for HIV dynamics. It is implemented in software available at [23]. The estimations results presented in Section 4.2 were directly obtained with this software. The reader can refer to refs. [24, 20-22] for further details on the identification technique.

6. Control Input

Usually, HIV / AIDS treatment takes place by some drugs known as RTI and PI. RTI, Inhibit produces new viruses by preventing recursive transcription (transcription reverse) of Viruses' RNA and turn it into their DNA, also slow infestation of process. Research shows that, the major impact of RTI is on the β parameters in model which used in [25-29]. On the other hand, PIs can effect on Viruses natural cycle life by prevent virus maturation process. As a result, new viruses lose the ability of infestation. Of course, PI's can Influence K parameter. S, δ, μ and C Parameters, according to their biological nature, do not affect process of treatment and medications [30]. If we show the impact of drugs on the model, equations (2) become equation (3).

$$\begin{aligned} \dot{x}_1 &= S - \delta x_1 - \bar{\beta} 3 x_1 x_3 \\ \dot{x}_2 &= \bar{\beta} x_1 x_3 - \mu x_2 \\ \dot{x}_3 &= \bar{k} x_2 - C x 3 \end{aligned} \tag{3}$$

In which $\bar{\beta}$, $\bar{k}$ introduce as $\bar{\beta} = (1 - \eta_{RTI})$ and $\bar{k} = (1 - \eta_{PI})$. Such that η_{RTI}, η_{PI} respectively reflects the impact of RI and PI. Thus, according to equation (2), mentioned system is a double-entry system. Considering the each amount of two prescribed medications, respectively, the new model obtained by equation (4).

$$\begin{aligned} \dot{x}_1 &= s - \delta x_1 - \rho(1-\mu_1)\beta x_1 x_3 \\ \dot{x}_2 &= \rho(1-\mu_1)\beta x_1 x_3 - \mu_2 x_2 \\ \dot{x}_3 &= \omega(1-\mu_2) k x_2 - \mu_1 x_3 \end{aligned} \tag{4}$$

According to research [31], u1 = 0.68 u u2 = 0.50 indicates the effect of each two types of drugs. They have no unit, and have real numbers between 0 and 1. If we do not use any medicine, put 0 related into their parameters. If any is used, equal by mentioned parameters (by effective drug parameter) which announced by its production company. However, no drug can completely eliminate HIV. Therefore every drug has partial effects on viruses and T lymphocytes. The effectiveness of each drug is equal by relative ability of T lymphocytes to destroy virus and patients. Effectiveness of prescribed medicines, displayed respectively, by the w and p parameters in reducing number of HIV contaminated T lymphocytes.

7. Linearization at Equilibrium Point

Based on obtained Characteristics of equation (4), the final equation, with its so-called equilibrium point or equilibrium condition, by some method can obtain non-linear function properly, one of these methods is Taylor series (with a few basic) by having trim point. In order to linearize general nonlinear systems, we

will use the Taylor Series expansion of functions. Consider a function f(x) of a single variable x, and suppose that x_0 is a point such that $f(x_0) = 0$. In this case, the point x_0 is called an equilibrium point of the system $\dot{x} = f(x)$, since we have $\dot{x} = 0$ when $x = x_0$ (i.e., the system reaches an equilibrium at x_0). Recall that the Taylor Series expansion of f(x) around the point x_0 is given by equation (5):

$$f(x)=\sum_{n=0}^{\infty}\frac{f^{(n)}x_0}{n!}(x-x_0)^n=f(a)+\frac{f'(a)}{1!}(x-a) \qquad (5)$$

For example, to show how the Taylor series work in linearization, we focus on hanging pendulum issue. The pendulum has released with initial angle **θ** by presence the friction in this case (Figure 2).

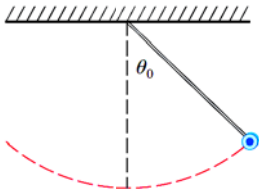


Fig. 2. hanging pendulum by friction

The device equivalent, with the presence of friction becomes equation (6).

$$\left.\begin{array}{c}\ddot{\theta}+0.5\theta+\sin\theta=0\\ \theta(0)=\frac{\pi}{2};\dot{\theta}=-1\\ x_1=\theta;x_2=\dot{\theta}\end{array}\right\}\Rightarrow f(x,t)=\begin{bmatrix}x_2\\ 0.5x_2-\sin x_1\end{bmatrix} \qquad (6)$$

Linear response of the system against speeches input, marked in Figure (3)

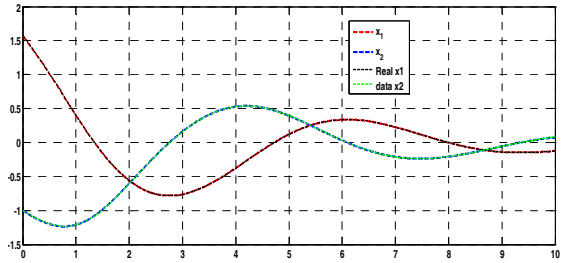


Fig. 3. original variable response and liberalized variable response

The new model of disease presented in Equation 3, is highly nonlinear. Thus based on Taylor series to useful trim point, ($x_1(0)$, $x_2(0)$, $x_3(0)$) , Transfer Matrix (A_1) and Input Matrix (B_1) have been gained.

$$x_1(0)=240, x_2(0)=21.6, x_3(0)=9.278$$

$$B_1=\begin{bmatrix}10\\0\\0\end{bmatrix}\quad A_1=\begin{bmatrix}-0.027 & 0 & -0.0019\\ 0.007 & -0.24 & 0.0019\\ 0 & 50w & -2.4\end{bmatrix}$$

The other hand, the output should be optimum means:

$$y=\begin{bmatrix}1000 & 100 & 0\end{bmatrix}\begin{bmatrix}x_1\\x_2\\x_3\end{bmatrix}+[0]\,u$$

According to medical constraints which preferred over mathematical models constraints, prescribed drugs ratio in the calculation of both drugs separately has worth more. Therefore, the amount of medication Number 1 (u_1) is chosen as a base. The amount of medication 2 (u_2) is calculated based on the former. Therefore, if a parameter related to the amount of medication that is equal to p, then we have a ratio equal to ***w*** is ***w*** to ***p***. In order to illustrate benefits of proposed mathematical model, the model must be stable. Therefore, it must be determined in a w range, which takes stability of system. To achieve this goal, we use Routh Horowitz benchmark. In criterion equation, characteristic equation is defined as $\det[A-\lambda I]$. In general, third order system characteristic equation considered by relationship (7):

$$\lambda^3+a_2\lambda^2+a_1\lambda+a_0=0 \qquad (7)$$

Coefficients are constant that depend on system parameters. The corresponding characteristic equation to equation (8) is:

$$\lambda^3+2.67\lambda^2+(0.65-0.1\times w)\lambda+(0.016-0.002\times w)a_0=0 \qquad (8)$$

If Routh Horowitz criterion used in below polynomial,

$$\left\{\begin{array}{l} 0.64 - 0.1w > 0 \Rightarrow w < 6.4 \\ 0.0016 - 0.002\,w > 0 \Rightarrow w < 8 \\ 0.65 - 0.1w > 0 \Rightarrow w < 6.5 \\ 0 < w < 6.4 \end{array}\right\} \quad (9)$$

The region of $\boldsymbol{0 < w < 6.4}$ is achieved, which corresponds to amount of negative Eigen value transfer matrix system. $\boldsymbol{W}$ After determining the state space systems for equation (10) are converted.

$$\begin{aligned} \dot{x} &= Ax + Bu \\ y &= Cx + Du \end{aligned} \quad (10)$$

System transfer function, derived as a parameter by equation (9) easily. Of course, for this purpose, can be used by MATLAB® software which results specified in the equation (11).

$$\frac{y(s)}{u(s)} = G(s) = \frac{(10\times(25000000\times w^2 + 1273450\times w + 288000))}{(755000\times w^2 + 330881\times w + 7776)} - \frac{(10\times(1197450\times w - 8400))}{(755000\times w^2 + 330881\times w + 7776)} \quad (11)$$

After that, the adaptive control system, which dynamically varies depending on the input, through adaptive control (Direct STR) input is applied, the output of dynamics a certain number of diseased and healthy cells are controlled.

8. Adaptive Self Tuning Regulator

In order to see the effectiveness of adaptive controller based on RLS-STR, we will use and the adaptive controller based on RLS-STR control algorithms to regulate the integrated resource and track performance: In many real problems, the workload cannot be measured real time or even cannot be measured. For such cases, the predictive control method cannot be applied. However, the adaptive controller can be designed, which can track the response time with estimating the system model meanwhile. According to this, we will design the RLS-STR for this problem. In the regression model (10), the orders are taken as p = 2, q = 2. Such a choice for the orders can maintain the tracking effect and hold the complexity of the problem. Then LS-STR is implemented by (12)–(19). In this episode we're going to design a Direct Adaptive controller by using pole placement and zero removal. As we know, in this way, no need to system parameters estimate, Diophantine equation solving even not get the controller parameters. In this way, controller parameters are estimated directly by RLS as shown in Figure (4).

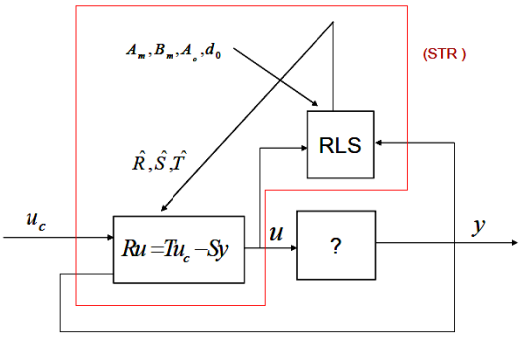


Fig. 4. Self Tuning Regulator or Direct Adaptive Controller

$$A_1 = \begin{bmatrix} -0.027 & 0 & -0.0019 \\ 0.007 & -0.24 & 0.0019 \\ 0 & 50\times\omega & -2.4 \end{bmatrix} \quad (12)$$

By applying a given input (5) which has three steps, change the dynamics of the system.

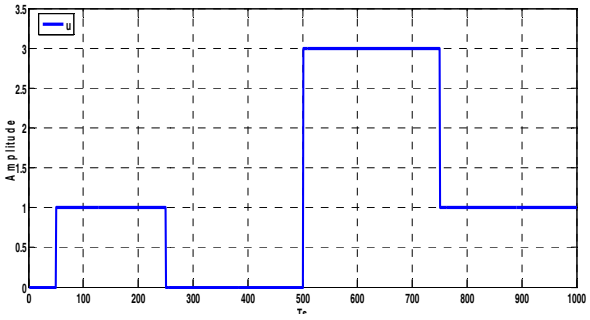


Fig. 5. Reference

In discrete mode, transfer function is obtained by 0.1 seconds sampling time that relationship between input and output will become by (15, 14, and 13). However, relationship between input and output in discrete mode for each of the three intervenes following links will become by (16, 17 and 18).

$$y(n) = 1.944\,y(n-1) - 0.948\,y(n-2) + 1.996\,u(n-1) - 1.9u(n-2) \quad (13)$$

$$y(n) = 2.56\,y(n-1) - 2.156\,y(n-2) + 0.5866\,y(n-3) + 1.996\,u(n-1) - 3.141u(n-2) + 1.176\,u(n-3) \quad (14)$$

$$y(n) = 2.575\,y(n-1) - 2.162\,y(n-2) + 0.586\,y(n-3) + 1.996\,u(n-1) - 3.152u(n-2) + 1.176\,u(n-3) \quad (15)$$

From these relationships, we use during program execution to update function. In design direct STR algorithm data is $A_0 \;\; B_m \;\; A_m \;\; d_0$. The desired system transfer functions due to compatibility condition for relations (16, 17 and 18) have been considered.

$$d_0 = 1 \quad (16)$$

$$\deg Am = \deg A$$
$$\deg Bm = \deg B \quad (17, 18)$$

8.1. Parameter Identification by RLS:

The identification algorithm is called Recursive Least square estimation algorithm, relations used in RLS method is determined in (19).

$$\hat{\theta} = \hat{\theta}(t-1) + k(t)e(t)$$
$$k(t) = p(t)\phi(t) = p(t-1)\phi(t)[\lambda I + \phi^T(t)p(t-1)\phi(t)]^{-1}$$
$$e(t) = y(t) - \phi^T(t)\hat{\theta}(t-1) \quad (19)$$
$$p(t) = [I - k(t)\phi^T(t)]\,p(t-1)/\lambda$$

Of course, display of system is specified in form (6), mainly incoming and outgoing system data give to RLS algorithm until parameter identified.

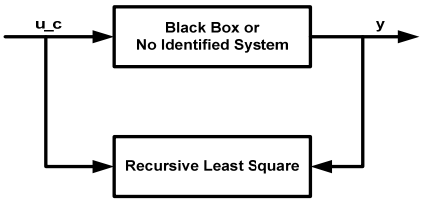


Fig. 6. RLS Algorithm

Where $\hat{\theta}$ is unknown parameters vector, e is error between estimated output and vector of actual system output, P is covariance matrix, control signal calculated by equation (20)

$$y(t) = R^* u_f(t-d_0) + S^* y_f(t-d_0)$$
$$u_f = \frac{1}{A_0(q^{-1})A_m(q^{-1})}u(t) \quad (20)$$
$$y_f = \frac{1}{A_0(q^{-1})A_m(q^{-1})}y(t)$$

y(t) is system output at time t where is equal by a multiple of control signal in addition by output filtered signal. As u_f is filtered control signal and y_f will be equal to filleted output signal. According to Figure 4 summarizes of direct STR algorithm is followed as:

1- Data information : A_m, B_m, A_0, d_0

2- $y(t) = R*u_f(t-d_0) + S*y_f(t-d_0)$ *and RLS* $\rightarrow \hat{\theta}$

3- $\hat{R}*u = T*u_c - \hat{S}*y, \;\; (T* = A_0^* A_m)$

4- Repeat again

The reason for using this algorithm can be simply reduce the size of its calculation noted. During the execution of this program will be used to update the $y\,[n\,]$ function [32].

9. Simulation and Result

In this section we discuss the evaluation and simulation of proposed system. Applied input to the system, will be in Figure (7).

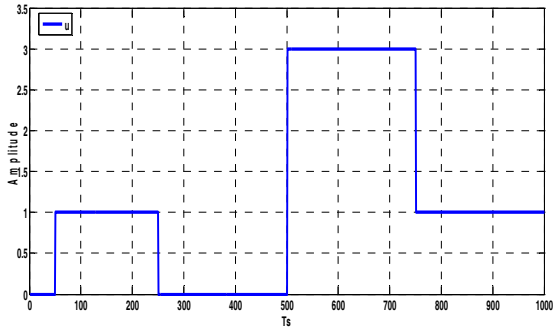
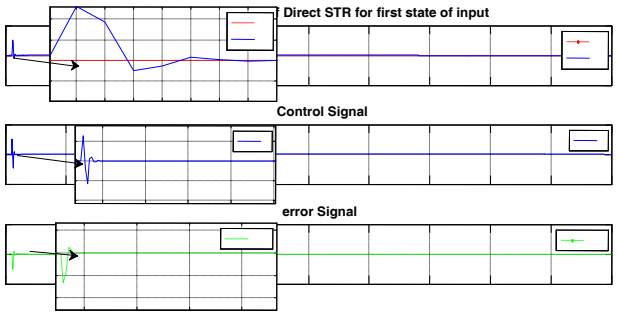


Fig. 7. Reference for Dynamic Adpting

In the first part the output of system will look for changes in basic mode, because of change dynamics of the system. By applying step, the dynamics will change the system displays the output, and error control signal in form (8) for only one entry will be displayed.



F ig. 8. output signal, control signal and error signal for first signal

In this section, reference input is x = 0,1,3, by applying dynamic entry, will have an impact in three section, certainly with regard to the three input output system (9), the control signal (10) and its error is specified in (11).

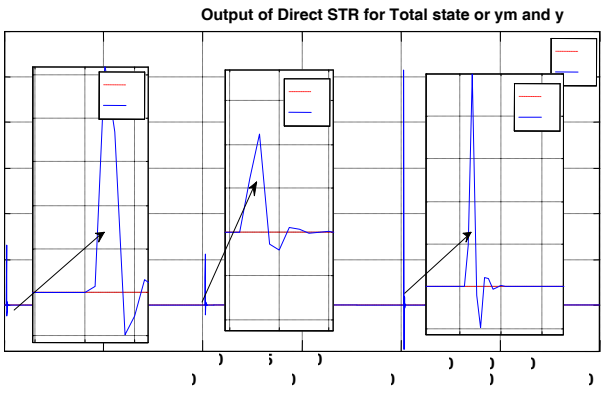


Fig. 9. Controlled output and Reference for each input

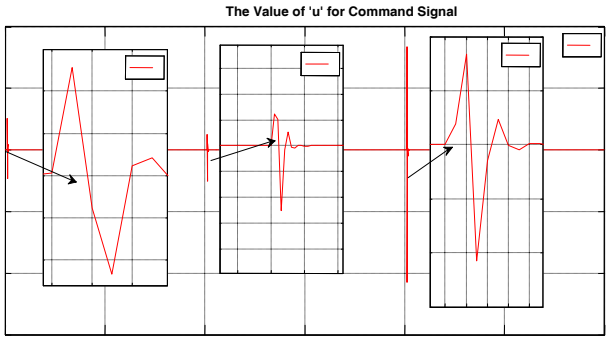


Fig. 10. control signal for each input

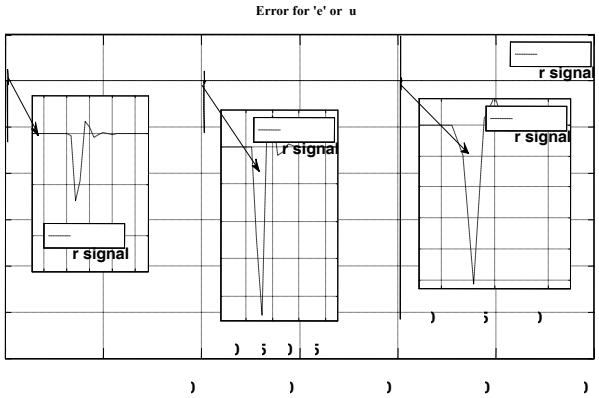


Fig. 11. error signal for each input

In three forms (8, 9, and 10) output values obtained, reference output, size and control signals as well as signals for input errors that changed dynamics of system was found to be limited, given well-known figures 8-10 proposed system has optimal performance due to input. Finally histogram of error specified is figure (13).

Fig. 12. error histogram

It is well known that performance was perfect because it revolves around zero point error has been

repeated many times. In order to study and performance system tracking, output or reference, we use following parameters, first parameter is MAE3 or mean absolute error (equation (21)), SSE4 parameter or sum of square errors (equation (22)) and third parameter mean square error (equation (23)) or MSE5 have been checked, and result in the formation (13) has been determined.

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(y_i - \overline{y}_i)^2 \quad (21)$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n}\left|(y_i - \overline{y}_i)\right| \quad (22)$$

$$SSE = \sum_{i=1}^{n}(y_i - \overline{y}_i)^2 \quad (23)$$

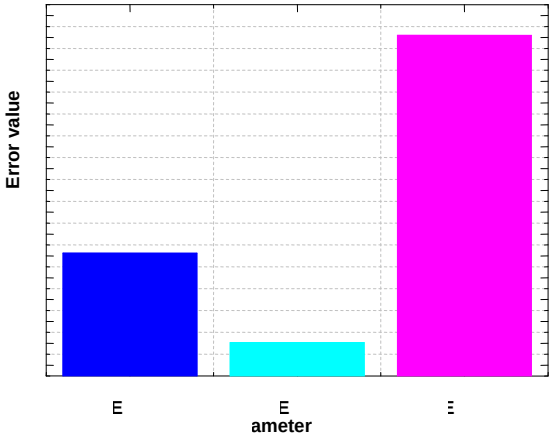


Fig. 13. errors bar

Of course, to enhance system performance, convergence parameters in figure (14) displayed, as well as the convergence it can be decided.

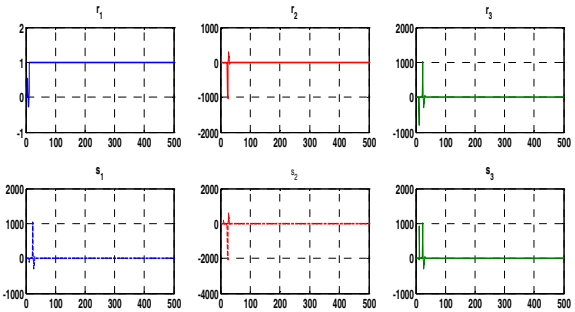


Fig. 14. Parameter Coverage

10. Conclusion

Based on real clinical data, the analysis of the impact of antiretroviral therapy on the HIV dynamics shows that the system is essentially a single input system in the sense that one single parameter is mostly affected by the drugs. After system identification (RLS) the single input model, parameter identified, and then controller based on system identification and control rule, adapted output to reference. In this paper, the parameter of the basic model of HIV/ AIDS is estimated only by measurement of the $CD4^{+}T$ cells and the viral load count. Since the suggested models for HIV, or infectious diseases like consumption, cholera, influenza and etc., have unknown parameters which should be estimated, one can use the proposed method in this paper to estimate the parameters of such models. One of the most important kinds of drug treatments for HIV immunotherapy is assumed. One can investigate the effects of other drugs, like Protease enzyme inhibitors in preventing AIDS progression. In these cases, one can use the STR controller method for solving such adaptive control problems.

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