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A Regulator Design for Nonlinear HIV-1 Infection System

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***Abstract*—In this paper a technique to control virus concentration for HIV-1 infection model obtained from actual patients data is introduced. The strategy is based on Linear quadratic regulator (LQR) and applied for each patient. Feedback linearization is also presented and preferred over other methods like the Taylor series, due to the fact that approximation around an operating point may not perform satisfactorily. The proposed controller has the ability to control the dynamic behavior of the virus concentration for different patients with the same control design. In addition, controller performance of both short and long term periods for each patient is evaluated.**

***Index Terms*—HIV-1 nonlinear model, Feedback linearization, Linear quadratic regulator (LQR), Nonlinear control.**

I. Introduction

IN the past years, many studies have sought to understand the basic characteristics of an HIV-1 dynamic infection model. Human immunodeficien y virus (HIV) infection can be characterized by three different stages, namely the acute infection, chronic infection, and acquired immunodeficien y syndrome (AIDS) [1]. During acute HIV infection, the viral load increases sharply in the firs few weeks, and then declines, ultimately reaching a quasi-steady state [2]–[5]. Decreasing the viral load from the peak is caused by immune cells response and/or limited target cell availability [6]. The viral steady state has been shown to predict the progress of further disease development [7]. The higher the viral steady state, the more quickly disease progresses to AIDS. Currently, there are four types of antiretroviral (ARV) drugs used in the treatment of HIV-1- patients. These include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry/fusion inhibitors (EIs). Each type of drug targets different stages of the viral lifecycle [8]. Antiretroviral therapy (ART) has used a combination of three or more drugs from two or more types. For example, a combination of two NRTIs with either a PI or NNRTI has proved to be extremely efficien in suppressing the plasma viral loads of most HIV-1-infected patients below the limit of viral detection (50 RNA copies ml^{-1}) by standard assay [9]. However, drug treatment often fails to achieve complete viral suppression to below the limit of detection because of many host and viral factors. For example, nonadherence to the dosing requirements, deleterious side effects, poor drug absorption and the emergence of a drug-resistant virus [10]. Therefore, controlling HIV infection has been an interesting problem for many researchers [11]–[18]. In this study, a transformed nonlinear HIV-1 model based on full state feedback control design for different patients is presented. The controller is then designed using the LQR technique to suppress the virus load to an undetectable level. Furthermore, HIV-1 virus concentration for different infected patients with LQR controller design is investigated in both short and long term periods.

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II. HIV-1 model system Definition

In this paper, we use a nonlinear HIV-1 model in [14] with control inputs introduced multiplicatively into the system. The corresponding control system can be represented as:

$$\begin{aligned} \dot{x}_1 = f_1(\cdot) &= \lambda - dx_1 - kx_1x_3 + kx_1x_3u_1 \\ \dot{x}_2 = f_2(\cdot) &= kx_1x_3 - \delta x_2 - kx_1x_3u_1 \\ \dot{x}_3 = f_3(\cdot) &= \pi x_2 - cx_3 - \pi x_2u_2 \end{aligned} \quad (1)$$

This model has three states that represent the primary dynamic of HIV-1 infection where x_1 denotes activated $CD4^+$T cells, x_2 is productively infected $CD4^+$ T cells and x_3 is the virus concentration. The parameter λ represents recruitment rate of activated $CD4^+$T cells, d is the death rate of activated $CD4^+$T cells, k is the rate of infection, δ is the death rate of $CD4^+$T infected cells, π is the rate of virus production by infected cells, c is the clearance rate of the virus, u_1 is T cells drug modulation and u_2 is virus drug modulation.

The estimated parameter values for different patients used in this study are shown in Table 1 [19].

The system in (1) can be transformed using the feedback linearization approach that will be discussed in more detail in the next section.

III. Feedback linearization approach

In this section, we develop a feedback linearized HIV-1 model. The feedback linearization has been described in the nonlinear control literature [20]–[22]. The idea is to algebraically transform a nonlinear system into an equivalent model of a linear form, and to cancel existing nonlinearities, such that linear control techniques can be applied.

Consider a square (same number of inputs and outputs) nonlinear system described by the following nonlinear differential equations:

TABLE I
PARAMETER VALUES FOR DIFFERENT PATIENTS

Patient	λ $cells\ ml\ day^{-1}$	d day^{-1}	k $ml\ viron\ day^{-1}$	δ day^{-1}	π $viron\ day^{-1}$
3	65	0.0065	$6.4 * 10^{-7}$	0.43	960
5	170	0.017	$6.3 * 10^{-7}$	0.39	870
6	120	0.012	$7.5 * 10^{-7}$	0.39	790
8	85	0.0085	$6.6 * 10^{-7}$	0.17	830

$$\dot{x} = f(x) + G(x)u = f(x) + \sum_{j=1}^{l} g(x)_j u_j \tag{2}$$

$$y = h(x) \tag{3}$$

where $x \in D \subset R^n$ is a state vector, $u \in R^l$ is a control input, y is an output of interest, and $f : D \subset R^n \rightarrow R^n$, $G \in R^{n\times l}$, and $h : D \subset R^n \rightarrow R^m$ are nonlinear functions of states in a smooth vector field respectively. Therefore, the system output can be differentiated until control inputs reappear.

$$y_m^{\rho_m} = L_f^{\rho_m} h_m + \sum_{j=1}^{l} L_{gj} L_f^{\rho_m - 1} h_m u_j \tag{4}$$

where lie derivatives are define as:

$$\begin{aligned} L_f^{\rho_m} h_m = L_f h_m (L_f^{\rho_m - 1} h_m) &= \frac{\partial (L_f^{\rho_m - 1} h_m)}{\partial x} f(x) \\ &= \left[\begin{array}{ccc} \frac{\partial (L_f^{\rho_m - 1} h_m)}{\partial x_1} & \ldots & \frac{\partial (L_f^{\rho_m - 1} h_m)}{\partial x_n} \end{array} \right] \left[\begin{array}{c} f_1 \\ \vdots \\ f_n \end{array} \right] \end{aligned} \tag{5}$$

Similarly:

$$\begin{aligned} L_g L_f^{\rho_m - 1} h_m &= \frac{\partial (L_f^{\rho_m - 1} h_m)}{\partial x} g(x) \\ &= \left[\frac{\partial (L_f^{\rho_m - 1} h_m)}{\partial x_1} \ldots \frac{\partial (L_f^{\rho_m - 1} h_m)}{\partial x_n} \right] \left[\begin{array}{c} g_1 \\ \vdots \\ g_n \end{array} \right] \end{aligned} \tag{6}$$

Hence, the equation (4) can be rewritten in a matrix form as

$$\left[\begin{array}{c} y_1^{\rho_1} \\ y_2^{\rho_2} \\ \vdots \\ y_m^{\rho_m} \end{array} \right] = \left[\begin{array}{c} L_f^{\rho_1} h_1 \\ L_f^{\rho_2} h_2 \\ \vdots \\ L_f^{\rho_m} h_m \end{array} \right] + \left[\begin{array}{cccc} L_{g_1} L_f^{\rho_1 - 1} h_1 & L_{g_2} L_f^{\rho_1 - 1} h_1 & \ldots & L_{g_l} L_f^{\rho_1 - 1} h_1 \\ L_{g_1} L_f^{\rho_2 - 1} h_2 & L_{g_2} L_f^{\rho_2 - 1} h_2 & \ldots & L_{g_l} L_f^{\rho_2 - 1} h_2 \\ \vdots & \vdots & \ldots & \vdots \\ L_{g_1} L_f^{\rho_m - 1} h_m & L_{g_2} L_f^{\rho_m - 1} h_m & \ldots & L_{g_l} L_f^{\rho_m - 1} h_m \end{array} \right] \left[\begin{array}{c} u_1 \\ u_2 \\ \vdots \\ u_l \end{array} \right] \tag{7}$$

$$\left[\begin{array}{c} y_1^{\rho_1} \\ y_2^{\rho_2} \\ \vdots \\ y_m^{\rho_m} \end{array} \right] \triangleq \left[\begin{array}{c} v_1 \\ v_2 \\ \vdots \\ v_m \end{array} \right] \tag{8}$$

According to nonlinear system theory, the number of derivatives needed to take from the output to get the control input is called the relative degree "ρ" of the system. Furthermore, if the total relative degree of the system is equal to the system degree itself, then the system can be fully feedback linearized. On the other hand, the system is partially feedback linearized when the system degree itself is greater than the relative degree of the system.

From (2) and (3), we can defin the HIV-1 system as:

$$f(x) = \left[\begin{array}{c} \lambda - dx_1 - kx_1x_3 \\ kx_1x_3 - \delta x_2 \\ \pi x_2 - cx_3 \end{array} \right], \; G(x) = \left[\begin{array}{cc} kx_1x_3 & 0 \\ -kx_1x_3 & 0 \\ 0 & -\pi x_2 \end{array} \right]$$

$$h(x) = \left[\begin{array}{c} x_2 \\ x_3 \end{array} \right]$$

Having taken the firs derivative from the output, we gain:

$$\begin{aligned} \dot{y} = \frac{\partial h}{\partial x} \dot{x} &= \left[\begin{array}{c} \dot{y}_1 \\ \dot{y}_2 \end{array} \right] \\ \dot{y} &= \left[\begin{array}{c} kx_1x_3 - \delta x_2 - kx_1x_3u_1 \\ \pi x_2 - cx_3 - \pi x_2 u_2 \end{array} \right] = \left[\begin{array}{c} v_1 \\ v_2 \end{array} \right] \end{aligned} \tag{9}$$

In the above firs derivative equation, the inputs appear and the relative degree of the system is two. Therefore, the total dynamics of the system can be divided into an external controlled part $(i.e.\xi)$ and an internal unobserved uncontrolled part $(i.e.\eta)$. Thus designing a controller for an external dynamic system is only applicable when the internal dynamic is stable, as shown below:

$$u = \frac{1}{L_g L_f^{\rho - 1} h(x)} [-L_f^{\rho} h(x) + v] = D^{-1}(x)[-b(x) + v] \tag{10}$$

Therefore, the coordinate transformation $Z = T(x)$ has been obtained in the following form as:

$$Z = T(x) = \begin{bmatrix} T_1(x) \\ T_2(x) \end{bmatrix} = \begin{bmatrix} y \\ \dot{y} \\ : \\ y^{\rho-1} \\ ... \\ \eta_1 \\ : \\ \eta_{(n-\rho)} \end{bmatrix}$$

$$= \begin{bmatrix} h(x) \\ L_f^1 h(x) \\ : \\ L_f^{\rho-1} h(x) \\ ... \\ \phi_1(x) \\ : \\ \phi_{(n-\rho)}(x) \end{bmatrix} = \begin{bmatrix} \xi_1 \\ \xi_2 \\ : \\ \xi_\rho \\ ... \\ \eta_1 \\ : \\ \eta_{(n-\rho)} \end{bmatrix} \tag{11}$$

where the components $\eta_1, \ldots, \eta_{(n-\rho)}$ of $\eta(x)$ are chosen such that $T(x)$ is a diffeomorphism in a domain $D_0 \subset D$ and:

$$\frac{\partial \phi_i(x)}{\partial x} G(x) = 0 \tag{12}$$

where $i = 1, 2, \ldots, n-\rho$, $\forall\ x \in D_0$. Then, we have :

$$Z = T(x) = \begin{bmatrix} T_1(x) \\ T_2(x) \end{bmatrix} = \begin{bmatrix} y_1 \\ y_2 \\ ... \\ \phi(x) \end{bmatrix} \tag{13}$$

To determine the normal form, equation (12) is applied as:

$$\begin{bmatrix} kx_1x_3 \frac{\partial \phi(x)}{\partial x_1} - kx_1x_3 \frac{\partial \phi(x)}{\partial x_2} & -\pi x_2 \frac{\partial \phi(x)}{\partial x_3} \end{bmatrix} = 0 \tag{14}$$

By using the separation of variables method, it yields:

$$\phi(x) = W(x_1 + x_2) \tag{15}$$

where W is a positive integer number, and $\phi(x)$ is nonunique.

After applying the coordinate transformation Z, it is possible to transform the nonlinear system to the following linear system:

$$\begin{bmatrix} \dot{\xi}_1 \\ \dot{\xi}_2 \\ \dot{\eta} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ d-\delta & 0 & -d \end{bmatrix} \begin{bmatrix} \xi_1 \\ \xi_2 \\ \eta \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ \lambda \end{bmatrix} \tag{16}$$

Fig. 1 shows block diagram for the HIV-1 control system with feedback linearization and LQR.

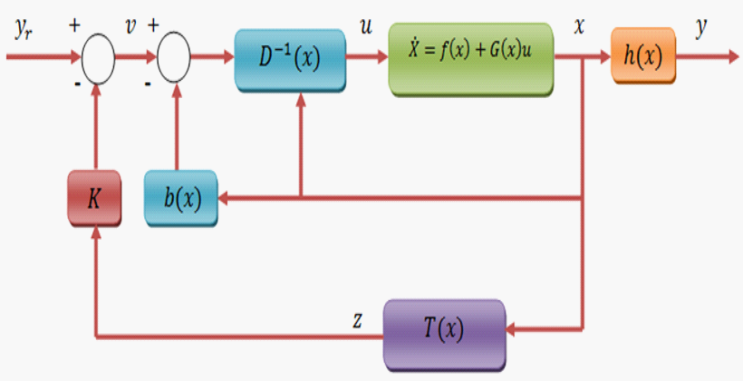

Fig. 1. HIV-1 control system with feedback linearization and LQR.

IV. Control Design Based on LQR

LQR is an optimal control scheme that gives best response with respect to some given measure of performance. The performance measure is a quadratic function composed of the state vector and control input. In this method, a feedback gain matrix is designed such that the performance measure is minimized. The performance measure is selected to achieve some compromise between the use of the control effort, the magnitude, and the speed of response that will guarantee system stability [23].

Consider an HIV-1 continuos linearized system for infected patients described in (16). In the LQR approach design problem, our goal is to construct a stabilizing linear state feedback controller of the form [24]:

$$v = -kZ = -kT(x) \tag{17}$$

where k is a constant control gain matrix.

$$u = D^{-1}(x)[-b(x) + v] \tag{18}$$

The performance measure is define as:

$$J = \int_0^\infty \left[x^T(t)Qx(t) + u^T(t)Ru(t)\right]\ dt \tag{19}$$

where Q is a symmetric positive semidefinit weighting matrix. R is a symmetric positive definit weighting matrix. The crucial task in designing an LQR is the selection of suitable weighting matrices for its performance measure such that the system's natural response is optimized.

The optimal control law, which minimizes J, has the form:

$$u_{op}(t) = -R^{-1}B^T P\ x(t) \tag{20}$$

where P is the symmetric positive definit solution of the Algebraic Riccati Equation (ARE):

$$A^T P + PA - PBR^{-1}B^T P + Q = 0 \tag{21}$$

In this design, the weighting matrices are chosen:

$$R = \begin{bmatrix} 1 & 0 \\ 0 & 0.00001 \end{bmatrix}, Q = \begin{bmatrix} q_{11} & 0 & 0 \\ 0 & q_{22} & 0 \\ 0 & 0 & q_{33} \end{bmatrix} \geq 0 \tag{22}$$

such that we want to drive $x_3(t)$ to zero. The rate $x_3(t) \to 0$ can be controlled by varying the numerical value of q. Here $(q_{11},\ q_{22},\ q_{33})$ are chosen as diag $(1, 100, 1)$.

V. Simulation and Results

The dynamics of HIV-1 virus concentration and transformed nonlinear HIV-1 model with LQR controller for different patients are simulated and presented in this section. The response of HIV-1 virus for different infected patients without external control is shown in Fig. 2.

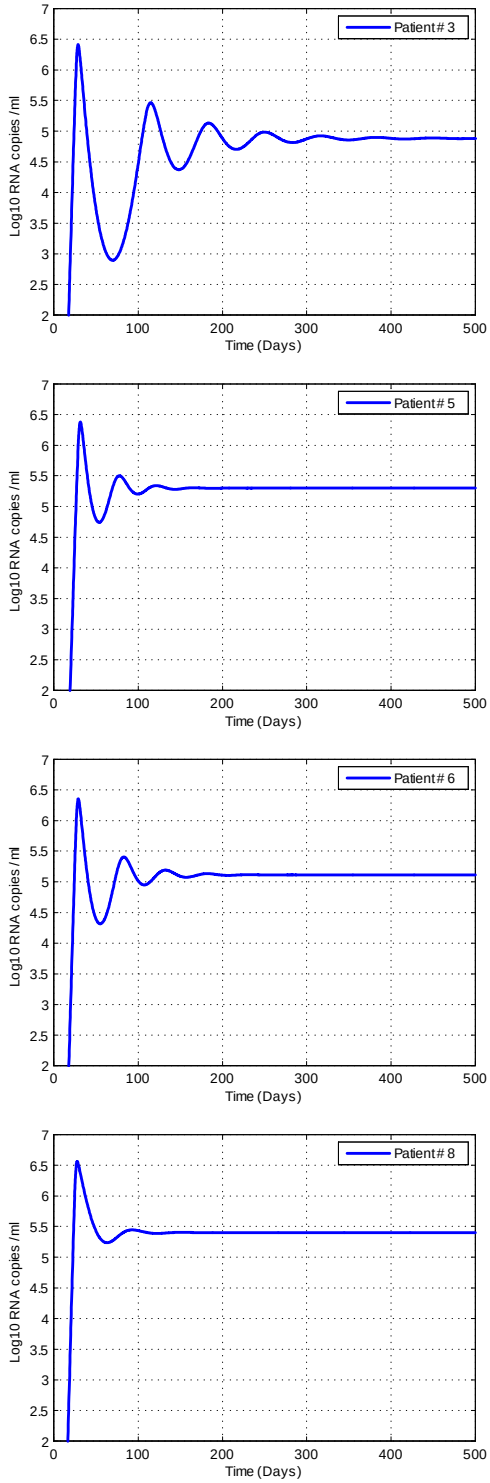

Fig. 2. HIV-1 virus concentration for different infected patients without external control.

For the different HIV-1 infected patients, a stabilizing linear state feedback controller is expressed in x-domain using (17) and (18) as:

$$u = D^{-1}(x)[-b(x) - kT(x)] \tag{23}$$

where:

$$D(x) = \begin{bmatrix} -kx_1x_3 \\ -\pi x_2 \end{bmatrix},\ b(x) = \begin{bmatrix} kx_1x_3 - \delta x_2 \\ \pi x_2 - cx_3 \end{bmatrix}, T(x) = \begin{bmatrix} x_2 \\ x_3 \\ \phi(x) \end{bmatrix}$$

By substituting (23) into (2) yields the closed loop nonlinear HIV-1 control system as:

$$\dot{x} = \begin{bmatrix} \lambda - dx_1 - kx_1x_3 \\ kx_1x_3 - \delta x_2 \\ \pi x_2 - cx_3 \end{bmatrix} + \begin{bmatrix} kx_1x_3 & 0 \\ -kx_1x_3 & 0 \\ 0 & -\pi x_2 \end{bmatrix} D^{-1}(x)[-b(x)+v] \tag{24}$$

Thus, we have

$$\dot{x} = \begin{bmatrix} \lambda - dx_1 - kx_1x_3 \\ kx_1x_3 - \delta x_2 \\ \pi x_2 - cx_3 \end{bmatrix} + \begin{bmatrix} kx_1x_3 & 0 \\ -kx_1x_3 & 0 \\ 0 & -\pi x_2 \end{bmatrix} \begin{bmatrix} -kx_1x_3 \\ -\pi x_2 \end{bmatrix}^{-1} [-\begin{bmatrix} kx_1x_3 - \delta x_2 \\ \pi x_2 - cx_3 \end{bmatrix} - k \begin{bmatrix} x_2 \\ x_3 \\ \phi(x) \end{bmatrix} \tag{25}$$

The simulated results in Fig. 3 and 4 show the control of the HIV-1 virus concentration for different infected patients with a controller that is designed using the LQR technique for short and long periods. It is assumed that the initial conditions when applying the control for infected patients is the steady states for each patient without control. The computational complexity of the controller design arises when HIV-1 system can only be partially feedback linearized. Therefore, the total dynamics of the system can be decomposed into an external controlled part $(i.e.\xi)$ and an internal unobserved uncontrolled part $(i.e.\eta)$. Also, findin the state transformation Z and construct function $\phi_1(x), \phi_2(x), ..., \phi_{n-\rho}(x)$ satisfying $\frac{\partial \phi_i(x)}{\partial x} G(x) = 0$ are being more difficul and complicated as described in section III.

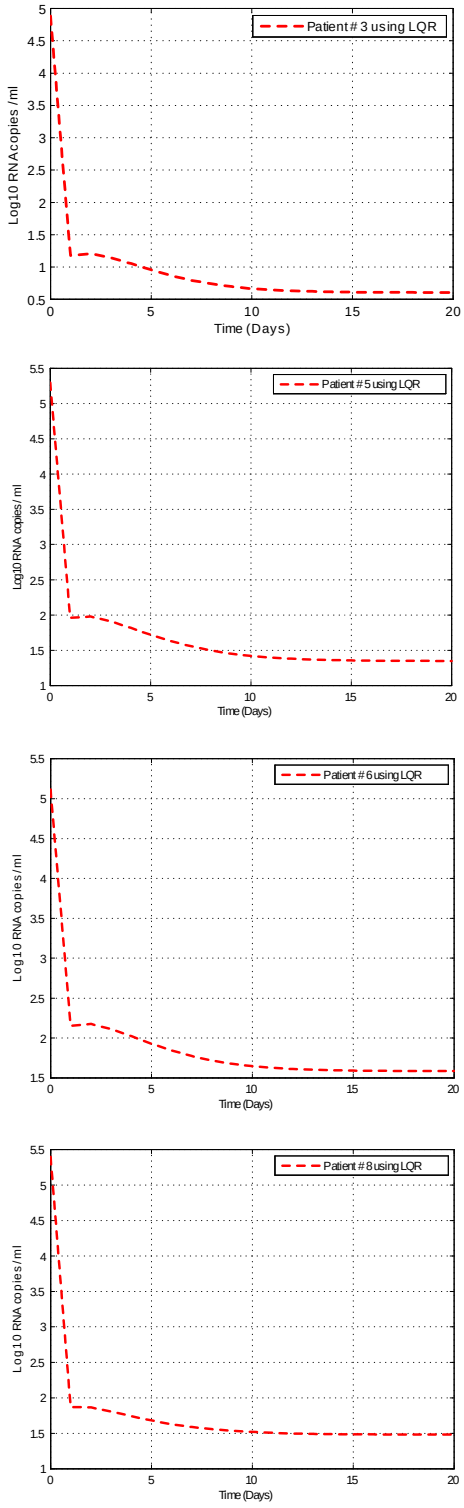

Fig. 3. HIV-1 virus concentration for different infected patients with LQR controller design for short term period.

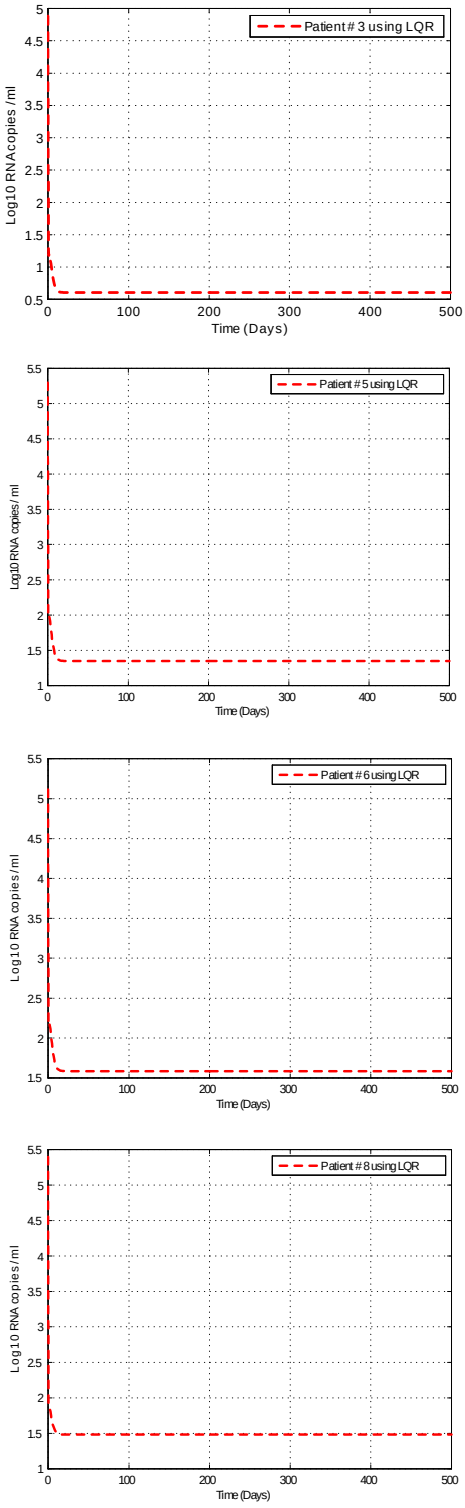

Fig. 4. HIV-1 virus concentration for different infected patients with LQR controller design for long term period.

VI. Conclusions and Future Work

In this study, the performance of an HIV-1 dynamic model for several patients based on full state feedback control design and real data is examined. A control strategy based on LQR is designed and evaluated for both short and long term periods. Feedback linearization is presented and preferred over other methods like the Taylor series because approximation around an operating point may not perform well. The results illustrate that the LQR technique based on feedback linearizing nonlinear HIV-1 model is effective in reducing virus concentration for each patient. Furthermore, the simulations show that LQR is a robust approach and can provide efficien results. However, the LQR may become hard to implement through drug regime.

In future work, the approach used in this study will be extended to more complex HIV-1 models like two strains HIV-1 model and time delay HIV-1 model.

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