

Nonlinear Uncertain HIV-1 Model Controller by Using Control Lyapunov Function

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ABSTRACT

In this paper, we introduce a new Control Lyapunov Function (CLF) approach for controlling the behavior of nonlinear uncertain HIV-1 models. The uncertainty is in decay parameters and also external control setting. CLF is then applied to different strategies. One such strategy considers input into infected cells population stage and the other considers input into a virus population stage. Furthermore, by adding noise to the HIV-1 model a realistic comparison between control strategies is presented to evaluate the system's dynamics. It has been demonstrated that nonlinear control has effectiveness and robustness, in reducing virus loading to an undetectable level.

Keywords: HIV-1 Infection Model; Control Lyapunov Function (CLF); Control Strategy; Uncertain Parameters; Noise Effect

1. Introduction

Modeling physical or biological phenomena for any dynamic system needs to take into account the nature of connection between the parameters of the dynamic system and the observed solution [1]. The function of these parameters is reflecting the characteristics of studied phenomena such that death rate of productive infected CD4⁺T cells for the HIV model. Therefore, it is valuable to know about how perturbations in these parameters present themselves in the solution. There are many papers for HIV modeling that consider the importance of parameters into a system's dynamic [2-4]. For example, in [5], a new mathematical model is presented to analyze many details on HIV-1 viral load data collected from five infected patients that were administrated using protease inhibitor. Based on data provided in [5], many viral dynamics that can not only give the kinetics dynamic of HIV-1 disease but also give guidelines to develop new treatment strategy are investigated. Controlling HIV infection disease has been an interesting problem for many researchers [6-11]. It is well known [12,13] that a control Lyapunov function, if available, will be a convenient tool to analyze stability, evaluate the system's robustness to perturbations, or even to modify the design to enhance robustness or performance [14]. In this paper, a CLF approach for nonlinear uncertain HIV-1 model is introduced. The uncertainty is applied into system's decay parameters and external control. Also, two different strategies based on CLF are investigated. It has been shown that the first

strategy is effective and has an ability to reduce virus concentration to an undetectable level even under uncertainty and noise effect.

2. Theory of Control Lyapunov Function (CLF)

A function $V(x)$ is said to be a Lyapunov function for a given system of vector state equations:

$$\dot{x} = F(x) \quad \text{with } F(0) = 0, \quad x \in R^n \quad (1)$$

If it is class C^1 and there exists a neighborhood Q of the origin such that [15]:

$$V(0) = 0 \quad \text{and } V(x) > 0 \quad \text{for } x \in Q, \quad x \neq 0 \quad (2)$$

$$\dot{V}(x) = \nabla V(x)F(x) < 0 \quad \text{for } x \in Q, \quad x \neq 0 \quad (3)$$

where: $\nabla V(x) = \left[\frac{\partial V(x)}{\partial x_1}, \frac{\partial V(x)}{\partial x_2}, \frac{\partial V(x)}{\partial x_3}, \dots, \frac{\partial V(x)}{\partial x_n} \right]$.

The classical Lyapunov stability theorem states that if Equation (1) has a suitable Lyapunov function, then the origin is globally asymptotically stable. Conversely, for any globally asymptotically stable system (1) with a continuous right hand side a Lyapunov function class C^∞ can be constructed.

If we consider the control system:

$$\dot{x} = f(x, u) \quad (4)$$

$x \in \Omega \in R^n$ is the state vector. $u \in R^m$ is the control

vector and is assumed continuously be stabilized. According to the above definition, a positive definite C^∞ function exists such that:

$$\inf (\nabla V(x) f(x, u)) < 0 \quad (5)$$

for each $x \neq 0$ in some neighborhood Q of the origin.

As a result, if the function $V(x)$ of class C^∞ satisfies Equations (2) and (5), then it's called a CLF [15].

3. Selection of Suitable CLF

It was shown in [16] that a first integral for the drift vector field, plus some controllability conditions can derive smooth asymptotically stabilizing control laws. This method has been introduced generally in [15,17], and is usually called Jurdjevic-Quinn method [14]. The control strategy based on this requires selection of CLF such that $V(x)$ is semi-positive definite. Stability is guaranteed if the derivative of $V(x)$ is semi-negative definite. Considering the following system (linear in control and non-linear in state):

$$\dot{x} = f_o(x) + \sum_{i=1}^m u_i f_i(x) \quad (6)$$

where $f_o(x)$ is a stable unforced system, u_i is the designated control, $f_i(x)$ is a smooth vector field in R^n .

We say that Equation (6) satisfies a Lyapunov condition of Jurdjevic-Quinn type if there are a neighborhood Q of the origin and a C^∞ function $V(x)$ such that [15]:

$$V(x) > 0 \text{ for } x \in Q, x \neq 0 \text{ and } V(0) = 0 \quad (7)$$

$$\nabla V(x) f_o(x) \leq 0 \text{ for } x \in Q \quad (8)$$

Now, the derivative of $V(x)$ with respect to the closed loop system is given by [15]:

$$\dot{V}(x) = \nabla V(x) f_o(x) - \sum_{i=1}^m [\nabla V(x) f_i(x)]^2 \leq 0 \quad (9)$$

According to the Lyapunov control, a control function is selected as following:

$$u_i(x) = -\nabla V(x) f_i(x), \quad i = 1, 2, \dots, m \quad (10)$$

4. Basic HIV-1 Infection Model

Parameters of HIV-1 infection models were estimated based on data provided by the Veterans Affairs hospital in West Haven, Connecticut, for a cohort of 338 people monitored for up to 2484 days [18]. This basic HIV-1 infection model is bilinear and has three states, namely uninfected cells (x), infected cells (y), and virus (v):

$$\begin{aligned} \dot{x} &= k_1 - k_2 x - k_3 x v \\ \dot{y} &= k_3 x v - k_4 y \\ \dot{v} &= k_5 y - k_6 v \end{aligned} \quad (11)$$

Let $x = [x_1, x_2, x_3]^T = [x, y, v]^T$ and let $(\cdot) = d(\cdot)/dt$, where $[\cdot]^T$ denotes transpose, Then:

$$\begin{aligned} \dot{x}_1 &= f_1(\cdot) = k_1 - k_2 x_1 - k_3 x_1 x_3 \\ \dot{x}_2 &= f_2(\cdot) = k_3 x_1 x_3 - k_4 x_2 \\ \dot{x}_3 &= f_3(\cdot) = k_5 x_2 - k_6 x_3 \end{aligned} \quad (12)$$

Figure 1 shows the dynamic response of HIV-1 infection model.

From Equation (12), k_1 is the supply rate of uninfected cells by the thymus, k_2 is the death rate of uninfected cells. k_3 is the rate of infection, k_4 is the death rate of infected cells, k_5 is the rate of virus production by infected cells, k_6 is the clearance rate of the virus. x_1 and x_2 are measured in (cells/mm³) and x_3 is measured in (particles/mm³). Also, from [18] we got **Table 1**.

5. Robust CLF Controller Design

Many control techniques have been applied for HIV treatment [19,20], but here we are interested to develop a new control design based CLF. A stabilizing state feedback law can be found via a suitable semi-definite positive function $V(x)$ in two assumed cases as:

$$\dot{x} = f_o(x) + \sum_{i=1}^m u_i f_i(x) = \begin{bmatrix} k_1 - k_2 x_1 - k_3 x_1 x_3 \\ k_3 x_1 x_3 - k_4 x_2 \\ k_5 x_2 - k_6 x_3 \end{bmatrix} + u_i f_i(x) \quad (13)$$

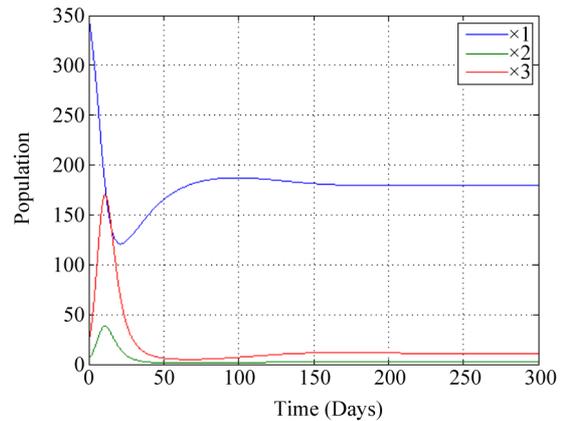


Figure 1. HIV-1 model without CLF, $x_1(0) = 350$, $x_2(0) = 5$, $x_3(0) = 25$. #

Table 1. Parameter values used in HIV-1 infection model.

Parameter	Value	Unit
k_1	10	cells mm ⁻³ day ⁻¹
k_2	0.05	day ⁻¹
k_3	5×10^{-4}	mm ³ cells ⁻¹ .day ⁻¹
k_4	0.4	day ⁻¹
k_5	40	day ⁻¹
k_6	9	day ⁻¹

The state feedback law with uncertainty is:

$$u_i(x_1, x_2, x_3) = -\nabla V(x_1, x_2, x_3) f_i(x, \Delta) \quad (14)$$

$V(x)$ from [21] is:

$$V(x, y, v) = x^* \left(\frac{x}{x^*} - \ln \frac{x}{x^*} \right) + y^* \left(\frac{y}{y^*} - \ln \frac{y}{y^*} \right) + \frac{k_4}{k_5} v^* \left(\frac{v}{v^*} - \ln \frac{v}{v^*} \right) \quad (15)$$

Now, we can express $V(x, y, v)$ as:

$$V(x_1, x_2, x_3) = x_1^* \left(\frac{x_1}{x_1^*} - \ln \frac{x_1}{x_1^*} \right) + x_2^* \left(\frac{x_2}{x_2^*} - \ln \frac{x_2}{x_2^*} \right) + \frac{k_4}{k_5} x_3^* \left(\frac{x_3}{x_3^*} - \ln \frac{x_3}{x_3^*} \right) \quad (16)$$

From $V(x_1, x_2, x_3)$ we can find $\nabla V(x_1, x_2, x_3)$:

$$\nabla V(x_1, x_2, x_3) = \left[\left(1 - \frac{x_1^*}{x_1} \right) \quad \left(1 - \frac{x_2^*}{x_2} \right) \quad \frac{k_4}{k_5} \left(1 - \frac{x_3^*}{x_3} \right) \right] \quad (17)$$

where $R_0 = \frac{k_1 k_3 k_5}{k_2 k_4 k_6}$, $x_1^* = \frac{k_1}{k_2 R_0}$,

$$x_2^* = \frac{k_2 k_6}{k_3 k_5} (R_0 - 1), \quad x_3^* = \frac{k_2}{k_3} (R_0 - 1)$$

From **Table 1** we can find R_0 and the equilibrium states:

$$R_0 = \frac{10}{9}, \quad x_1^* = 180, \quad x_2^* = 2.5, \quad x_3^* = \frac{100}{9}$$

5.1. Applying Control Strategy into Infected Cells with Uncertainty

In this section, we can apply the control input to infected cells for HIV-1 infection model with uncertainty as:

$$\dot{x} = f_o(x, \Delta) + \sum_{i=1}^m u_i f_i(x, \Delta) = \begin{bmatrix} k_1 - (k_2 \pm \Delta)x_1 - k_3 x_1 x_3 \\ k_3 x_1 x_3 - (k_4 \pm \Delta)x_2 \\ k_5 x_2 - (k_6 \pm \Delta)x_3 \end{bmatrix} + u_1 \begin{bmatrix} 0 \\ (k_6 \pm \Delta)x_2 \\ 0 \end{bmatrix} \quad (18)$$

In this case, $u_1(x_1, x_2, x_3)$ will be:

$$u_1(x_1, x_2, x_3) = - \left[\left(1 - \frac{x_1^*}{x_1} \right) \quad \left(1 - \frac{x_2^*}{x_2} \right) \quad \frac{(k_4 \pm \Delta)}{(k_5 \pm \Delta)} \left(1 - \frac{x_3^*}{x_3} \right) \right] \begin{bmatrix} 0 \\ (k_6 \pm \Delta)x_2 \\ 0 \end{bmatrix} \quad (19)$$

$$u_1(x_1, x_2, x_3) = -(k_6 \pm \Delta)x_2 \left(1 - \frac{x_2^*}{x_2} \right) \quad (20)$$

5.2. Applying Control Strategy into Virus with Uncertainty

We can also apply the control input to virus for the HIV-1 infection model with uncertainty as:

$$\dot{x} = f_o(x, \Delta) + \sum_{i=1}^m u_i f_i(x, \Delta) = \begin{bmatrix} k_1 - (k_2 \pm \Delta)x_1 - k_3 x_1 x_3 \\ k_3 x_1 x_3 - (k_4 \pm \Delta)x_2 \\ k_5 x_2 - (k_6 \pm \Delta)x_3 \end{bmatrix} + u_1 \begin{bmatrix} 0 \\ 0 \\ x_3 \end{bmatrix} \quad (21)$$

In this case, $u_1(x_1, x_2, x_3)$ will be:

$$u_1(x_1, x_2, x_3) = - \left[\left(1 - \frac{x_1^*}{x_1} \right) \quad \left(1 - \frac{x_2^*}{x_2} \right) \quad \frac{(k_4 \pm \Delta)}{(k_5 \pm \Delta)} \left(1 - \frac{x_3^*}{x_3} \right) \right] \begin{bmatrix} 0 \\ 0 \\ x_3 \end{bmatrix} \quad (22)$$

$$u_1(x_1, x_2, x_3) = -x_3 \frac{(k_4 \pm \Delta)}{(k_5 \pm \Delta)} \left(1 - \frac{x_3^*}{x_3} \right) \quad (23)$$

6. Noise Effect on HIV-1 Dynamic System

In this section, noise effect on HIV-1 dynamic system with external control input is investigated into two strategies as:

$$\dot{x} = f_o(x) + \sum_{i=1}^m u_i f_i(x) + d = \begin{bmatrix} k_1 - k_2 x_1 - k_3 x_1 x_3 \\ k_3 x_1 x_3 - k_4 x_2 \\ k_5 x_2 - k_6 x_3 \end{bmatrix} + u_i f_i(x) + d \quad (24)$$

where d represents noise effect.

7. Simulation and Results

In **Figure 2**, it is assumed a ($\pm 5\%$) deterministic uncertainty in decay parameters of HIV-1 model are related to the first strategy. It's noted that uncertainty doesn't affect the control role on reducing viral load to an undetectable level, however the number of healthy cells with (+5%) uncertainty is reduced and with (-5%) uncertainty is increased and this can be referred to detrimental and beneficial perturbation respectively.

In **Figure 3**, it is assumed a high deterministic uncertainty ($\pm 20\%$) in decay parameters of HIV-1 model are related to the first strategy. It is noted that even for high uncertainty, the control is still effective on reducing viral load to an undetectable level, however the number of healthy cells with (+20%) and (-20%) uncertainty is reduced (detrimental perturbation) and increased (beneficial perturbation) respectively.

In **Figure 4**, it is assumed a ($\pm 5\%$) deterministic uncertainty in decay parameters of HIV-1 model are related

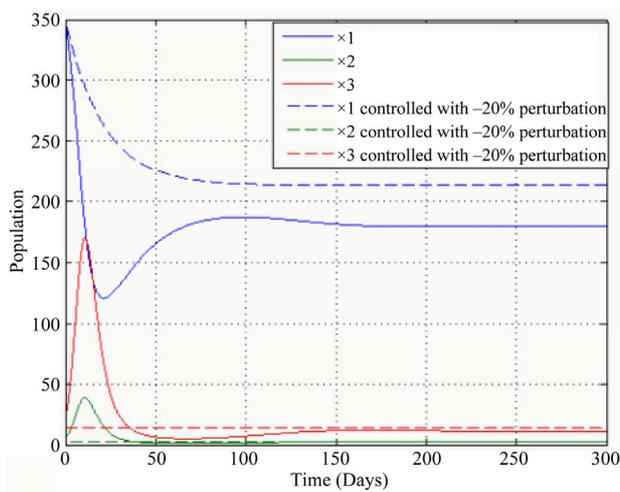
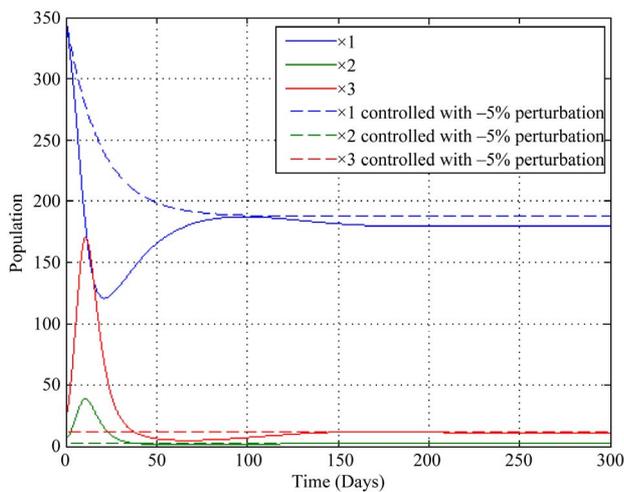
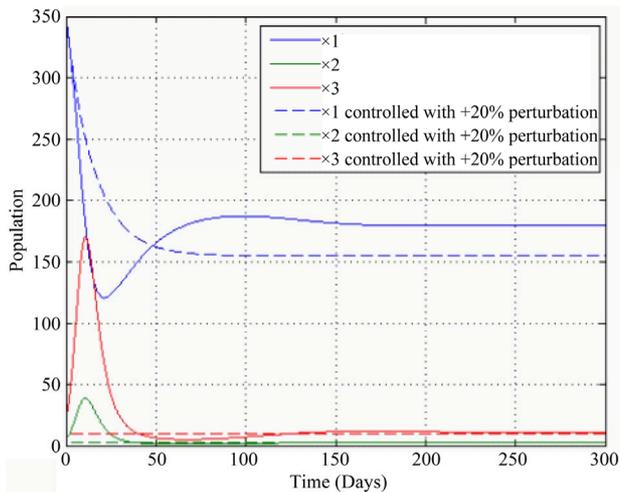
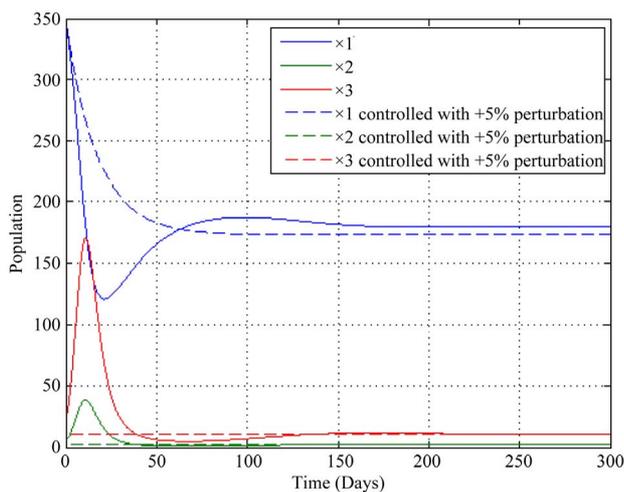
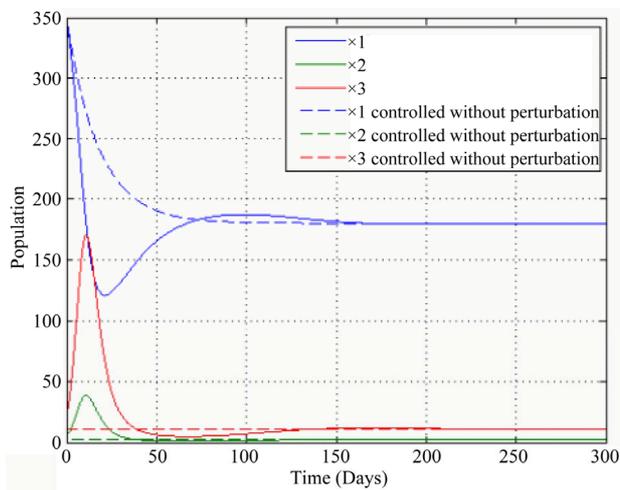
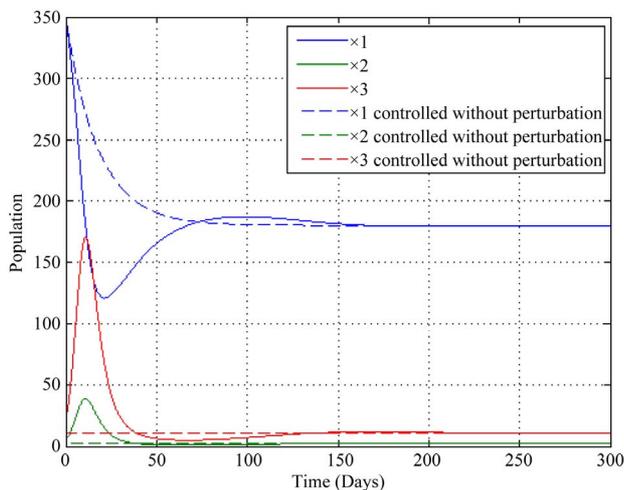


Figure 2. Control performance for nonlinear HIV-1 model under $\pm 5\%$ deterministic parameters uncertainty for first strategy.

Figure 3. Control performance for nonlinear HIV-1 model under $\pm 20\%$ deterministic parameters uncertainty for first strategy.

to the second strategy. It's noted that uncertainty affect the control role on reducing viral concentration to an undetectable level which means that the first strategy is more efficient than second strategy.

In **Figure 5**, it is assumed a high ($\pm 20\%$) deterministic uncertainty in decay parameters of HIV-1 model are related to the second strategy. It's noted at high uncertainty, the control effect becomes worse on reducing viral con-

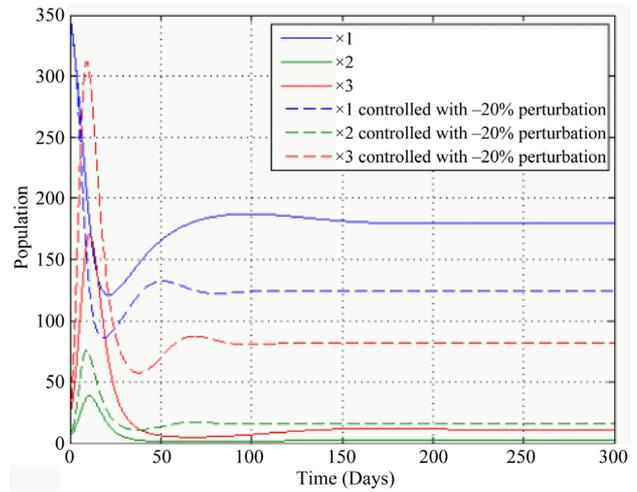
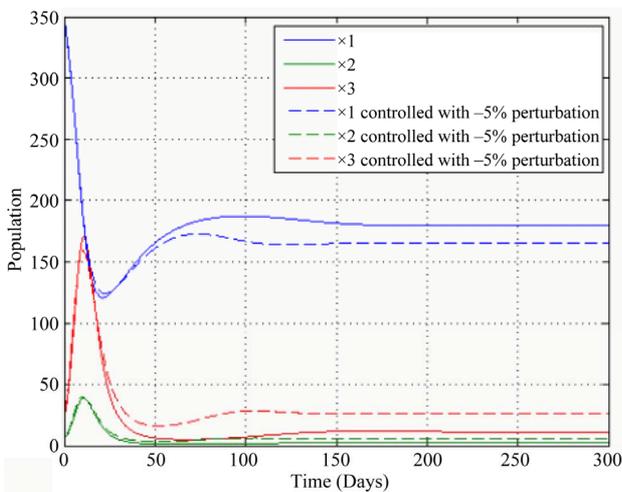
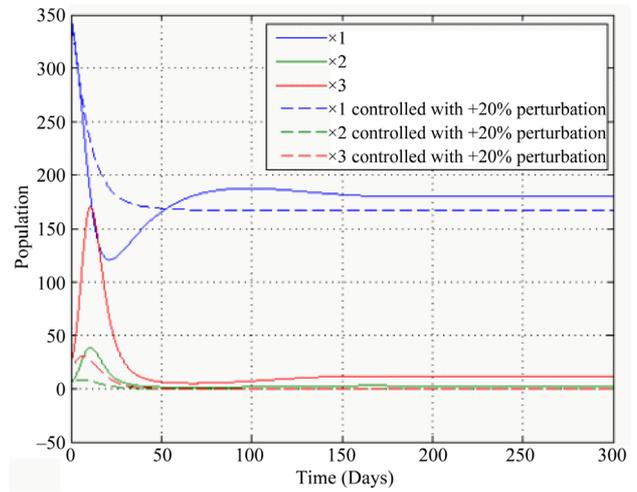
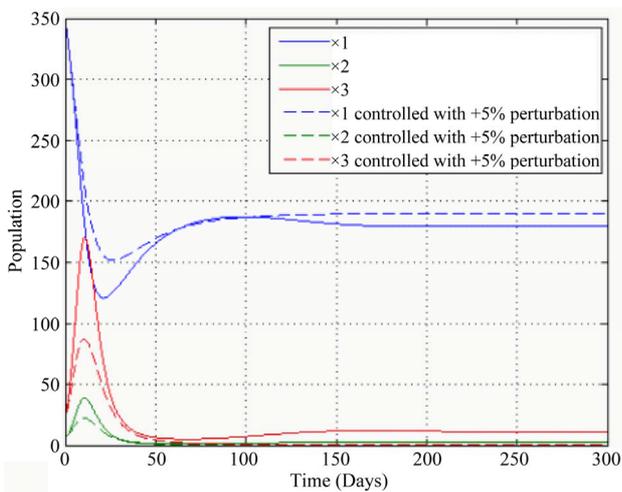
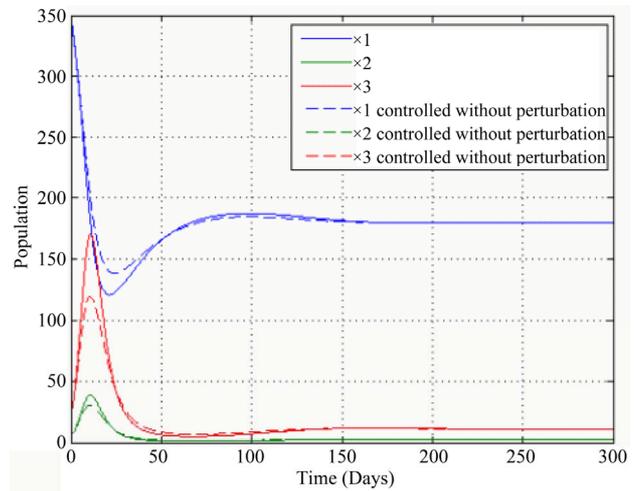
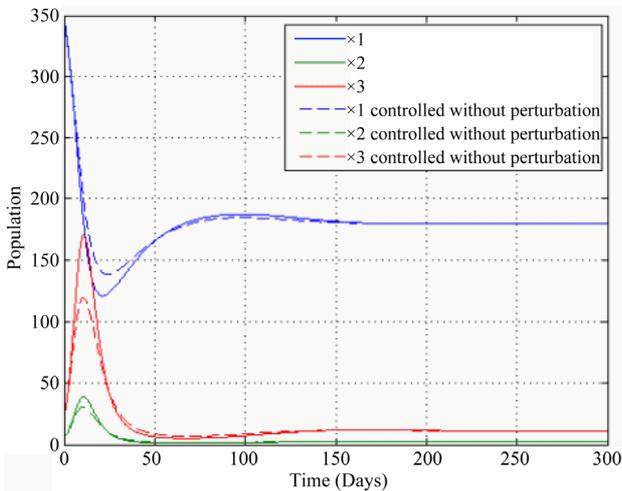


Figure 4. Control performance for nonlinear HIV-1 model under $\pm 5\%$ deterministic parameters uncertainty for second strategy.

Figure 5. Control performance for nonlinear HIV-1 model under $\pm 20\%$ deterministic parameters uncertainty for second strategy.

centration.

In **Figure 6**, we add a constant noise (+10) in HIV-1 model related to first and second strategy. It's shown that noise has a little impact on the HIV-1 system dynamic

and that is also depends on how much noise is added.

8. Conclusion

This paper has presented a new robust CLF control de-

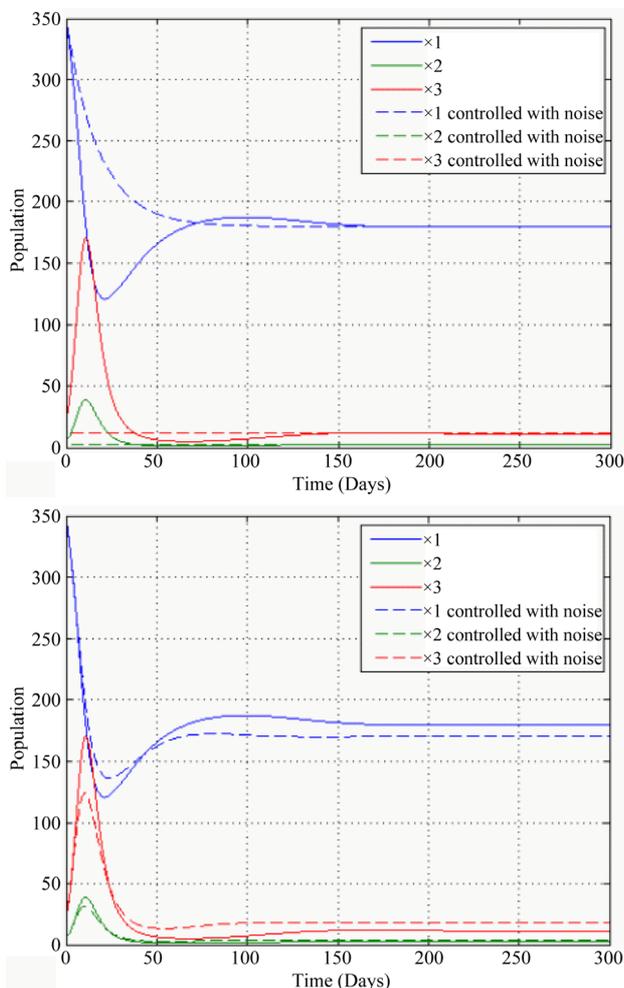


Figure 6. Noise effect on nonlinear HIV-1 model for first and second strategies respectively.

sign for uncertain and nonlinear HIV-1 infection models. We have found suitable nonlinear controller strategy to cause reduction of virus concentration to an undetectable level. Different strategies were considered to evaluate the control effectiveness. Additional noise into the HIV-1 system's dynamics was simulated to further test the nonlinear control strategies stochastic behavior.

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