Is the HIV therapy system chaotic?

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Abstract

In this paper, we show numerically that the so-called *HIV therapy system* is regular and converges to a stable equilibrium point for most realistic values (in the medical sense) of its bifurcation parameters. Although there is no rigorous proof of this convergence property, it is conjectured that the system is not chaotic for all positive bifurcation parameters.

Keywords: HIV therapy system, no chaos, convergence to equilibria.
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1 Introduction

Today, the human immunodeficiency virus (HIV) is the most dangerous and killing disease, and there are millions of infected people. The dynamics of the HIV therapy system is given by the following first-order nonlinear differential equation [Filter *et al.*, 2005; Xia & Moog, 2003; Hammond, 1993; Wein *et al.*, 1997; de Boer & Perelson, 1998; Wein *et al.*, 1998; Dixit & Perelson, 2004; Strafford *et al.*, 2000; Fishman & Perelson, 1994; Essunger & Perelson, 1994; Berry & Nowak, 1994; Lipsitch & Nowak, 1995; Nowak *et al.*, 1995;

Courchamp *et al.*, 1995; Iwasa *et al.*, 2005; Nowak *et al.*, 1997; Wodarz *et al.*, 1999; Gilchrist *et al.*, 2004; Jafelice *et al.*, 2004]:

$$\begin{cases} x' = a\left(x_0 - x\right) - bxz \\ y' = c\left(y_0 - y\right) + dyz \\ z' = z\left(ex - fy\right) \end{cases} \tag{1}$$

where $(a, b, c, d, e, f) \in \mathbb{R}^6$ are positive bifurcation parameters. The variables $x(t), y(t)$, and $z(t)$ are the concentrations of the CD4 lymphocyte population, the CD8 lymphocyte population, and the HIV-1 viral load, respectively. The positive quantities x_0 and y_0 are the normal unperturbed concentrations of the CD4 and CD8 lymphocyte population, respectively. The system (1) has two equilibria

$$\begin{cases} P_1 = (x_0, y_0, 0) \\ P_2 = \left(\frac{adx_0e+bcfy_0}{e(ad+bc)}, \frac{eadx_0+bcfy_0}{adf+bcf}, \frac{ac(x_0e-fy_0)}{adx_0e+bcfy_0}\right) = (u, v, w) \end{cases} \tag{2}$$

in which P_1 is stable when $ex_0 - fy_0 < 0$ and unstable when $ex_0 - fy_0 > 0$. From our numerical calculations, we observe that system (1) always converges to the equilibrium point P_2. The stability of P_2 can be studied using the Jacobian matrix given by:

$$J\left(P_2\right) = \begin{pmatrix} -a - bw & 0 & -bu \\ 0 & -c + dw & dv \\ ew & -fw & eu - fv \end{pmatrix} \tag{3}$$

The characteristic polynomial at P_2 is given by $\lambda^3 + A\lambda^2 + B\lambda + C = 0$, where

$$\begin{cases} A = a + c - ue + bw - dw + fv \\ B = ac - bdw^2 - aue - cue - adw + bcw + afv + cfv + duwe + bfvw \\ C = -acue + acfv + aduwe + bcfvw \end{cases} \tag{4}$$

The exact values of the eigenvalues can be obtained using Cardano's method for solving a cubic equation, but due to the complicated formulas in this case, we use the Routh-Hurwitz stability criterion, leading to the conclusion that the real parts of the roots λ are negative if and only if $A > 0$, $C > 0$, and $AB - C > 0$. Thus P_2 is stable if and only if

$$\begin{cases} a + c - ue + bw - dw + fv > 0 \\ acfv - acue + aduwe + bcfvw > 0 \\ \mu_1 + \mu_2 + \mu_3 + \mu_4 + \mu_5 + \mu_6 + \mu_7 > 0 \end{cases} \tag{5}$$

where

$$\begin{cases} \mu_1 = a^2c - a^2dw + a^2fv - ea^2u + 2abcw - 2abdw^2 \\ \mu_2 = 2abfvw - eabuw + ac^2 - 2acdw + 2acfv - 2eacu + ad^2w^2 \\ \mu_3 = -2adfvw + 2eaduw + af^2v^2 - 2eafuve^3au^2 + b^2cw^2 \\ \mu_4 = -b^2dw^3 + b^2fvw^2 + bc^2w - 2bcdw^2 + 2bcfvw - 2ebcuw \\ \mu_5 = bd^2w^3 - 2bdfvw^2 + 2ebduw^2 + bf^2v^2w - ebfuvw \\ \mu_6 = c^2fv - ec^2u - cdfvw + 2ecduw + cf^2v^2 \\ \mu_7 = -2ecfuv + e^3cu^2 - ed^2uw^2 + edfuvw - e^3du^2w \end{cases} \tag{6}$$

We note that it is not easy to solve such inequalities. The simple way is to consider some particular values of the eight parameters and vary each one of them as shown in the next section.

2 Is the HIV therapy system chaotic?

It was claimed in [Charlotte & Bingo, 2010] that the dynamics of the HIV system (1) is chaotic by calculating its Lyapunov exponents. Apparently this solution is only transiently chaotic. In fact, we show numerically that system (1) is not chaotic for $a = 0.25, b = 50, c = 0.25, e = 0.01, f = 0.006, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0, z(0) = 0.03$, and $0 < d < 50$ as shown in Fig. 1.

In this case, there is only a single stable equilibrium with a negative largest Lyapunov exponent (L) and no indication of multistability. Numerical calculations confirm that this stable equilibrium is $P_2 = \left(\frac{1000.0d+16500.0}{d+50.0}, \frac{2.5d+41.25}{0.0015d+0.075}, \frac{0.41875}{2.5d+41.25}\right)$.

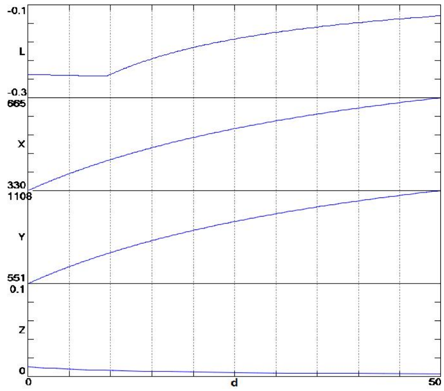

Figure 1: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $d \in [0, 50]$ for $a = 0.25, b = 50, c = 0.25, e = 0.01, f = 0.006, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

It is easy to verify that the first and the second components of P_2 are increasing, and the third one is decreasing with respect to the variations of d, that is $\frac{d}{d(d)}\left(\frac{1000.0d+16500.0}{d+50.0}\right) = \frac{33500.0}{d^2+100.0d+2500.0} > 0$, $\frac{d}{d(d)}\left(\frac{2.5d+41.25}{0.0015d+0.075}\right) = \frac{1.675\times10^5}{3.0d^2+300.0d+7500.0} > 0$ and $\frac{d}{d(d)}\left(\frac{0.41875}{2.5d+41.25}\right) = -\frac{1.0469}{(2.5d+41.25)^2} < 0$. The graphs of these functions (versus d) are in agreement with the bifurcation diagrams shown in Fig. 1. This method is also used for all other bifurcation parameters to show the convergence of system (1) to its equilibrium point P_2. To prove this result, we have from the above analysis

$$\begin{cases} A = \frac{3325.0d+1.6625\times10^5}{5000(2.0d+33.0)} \\ B = \frac{6.749\times10^9 d+2.8424\times10^8 d^2+3.3913\times10^6 d^3+5.0759\times10^{10}}{500\,000(d+50.0)(2.0d+33.0)^2} \\ C = \frac{1675.0d+83752.}{4000(d+50.0)} \end{cases} \tag{7}$$

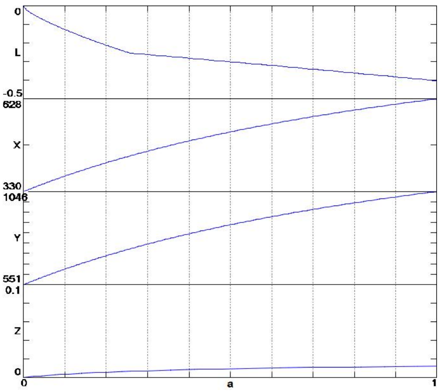

Figure 2: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $a \in [0, 1]$ for $b = 50, c = 0.25, d = 10, e = 0.01, f = 0.006, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

so that P_2 is stable if and only if

$$\left\{ \begin{array}{c} \frac{3325.0d+1.6625\times10^5}{2.0d+33.0} > 0 \\ \\ \frac{1675.0d+83752.}{d+50.0} > 0 \\ \\ \frac{3.6446\times10^{11}d+1.6851\times10^{10}d^2+2.7023\times10^8d^3+1.1604\times10^6d^4+2.623\times10^{12}}{1000000(d+50.0)(2.0d+33.0)^3} > 0 \end{array} \right. \tag{8}$$

which proves that P_2 is stable for all $d > 0$. The same analysis can be done for the other parameters, and the behavior of system (1) can be seen in Figs. 2–8.

In addition, we examined approximately 10^7 instances of (1) with random values of the eight parameters, chosen from a Gaussian distribution with mean 1 and variance 1, and did not find a single case with a positive Lyapunov exponent. Thus we conclude that the HIV therapy system (1) is almost certainly regular and converges to its stable equilibrium point P_2 for all a, b, c, d, e, f, x_0, and y_0 in the indicated ranges, and we advance the following conjecture:

Conjecture 1 *The HIV therapy system (1) converges to its stable equilibrium point P_2 for all a, b, c, d, e, f, x_0 and y_0.*

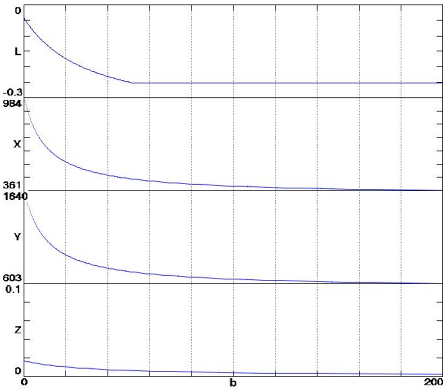

Figure 3: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $b \in [0, 200]$ for $a = 0.25, c = 0.25, d = 10, e = 0.01, f = 0.006, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

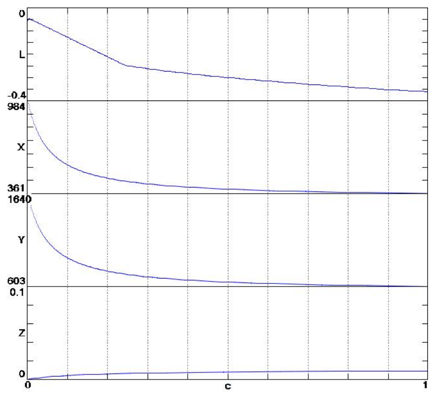

Figure 4: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $c \in [0, 1]$ for $a = 0.25, b = 50, d = 10, e = 0.01, f = 0.006, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

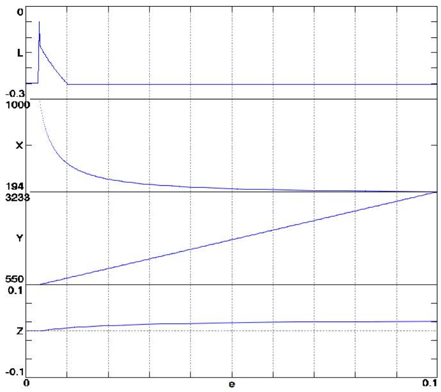

Figure 5: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $e \in [0, 0.1]$ for $a = 0.25, b = 50, c = 0.25, d = 10, f = 0.006, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

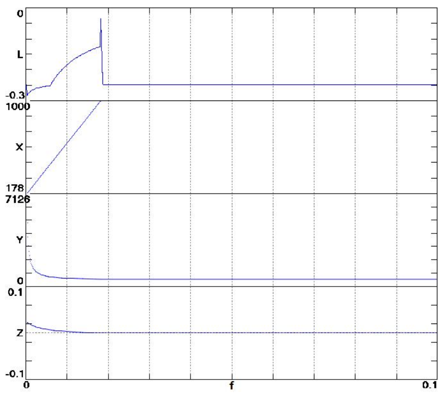

Figure 6: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $f \in [0, 0.1]$ for $a = 0.25, b = 50, c = 0.25, d = 10, e = 0.01, x_0 = 1000, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

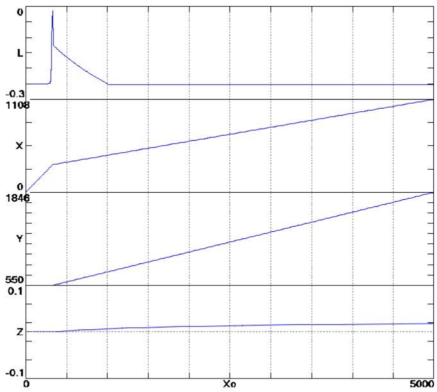

Figure 7: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $x_0 \in [0, 5000]$ for $a = 0.25, b = 50, c = 0.25, d = 10, e = 0.01, f = 0.006, y_0 = 550, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

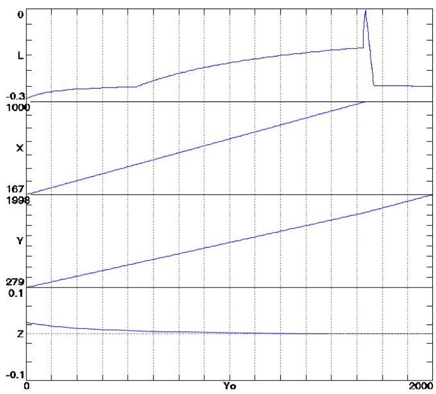

Figure 8: Bifurcation diagram of the variables x, y, and z (with the variation of the largest Lyapunov exponent L) of system (1) plotted versus $y_0 \in [0, 2000]$ for $a = 0.25, b = 50, c = 0.25, d = 10, e = 0.01, f = 0.006, x_0 = 1000, x(0) = x_0, y(0) = y_0$, and $z(0) = 0.03$.

As a result of the previous conjecture, we conclude that the concentration of the CD4 lymphocyte population converges to the fixed quantity $\frac{adx_0e+bcfy_0}{e(ad+bc)}$, the CD8 lymphocyte population converges to $\frac{eadx_0+bcfy_0}{adf+bcf}$, and the HIV-1 viral load converges to $\frac{ac(x_0e-fy_0)}{adx_0e+bcfy_0}$ with the condition $x_0e - fy_0 > 0$ since it is a positive quantity. In this case, the system (1) never converges to P_1 because it is always unstable. Thus the system (1) never returns to the normal unperturbed concentrations of the CD4 and CD8 lymphocyte populations denoted by x_0 and y_0.

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