MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **3**, Number **2**, April **2006**

http://www.mbejournal.org/

pp. **313–324**

MODELING CANCER IN HIV-1 INFECTED INDIVIDUALS: EQUILIBRIA, CYCLES AND CHAOTIC BEHAVIOR

Jie Lou

Department of Mathematics, Shanghai University,
99 Shangda Road Shanghai 200444, P. R. China

Tommaso Ruggeri

Department of Mathematics and
Research Center of Applied Mathematics (CIRAM)
University of Bologna, Via Saragozza 8, 40123 Bologna, Italy

Claudio Tebaldi

Department of Mathematics, Politecnico of Torino,
Corso Duca degli Abruzzi 24, 10129 Torino, Italy

(Communicated by Yang Kuang)

Abstract. For HIV-infected individuals, cancer remains a significant burden. Gaining insight into the epidemiology and mechanisms that underlie AIDS-related cancers can provide us with a better understanding of cancer immunity and viral oncogenesis. In this paper, an HIV-1 dynamical model incorporating the AIDS-related cancer cells was studied. The model consists of three components, cancer cells, healthy CD4+ T lymphocytes and infected CD4+ T lymphocytes, and can have six steady states. We discuss the existence, the stability properties and the biological meanings of these steady states, in particular for the positive one: cancer-HIV-healthy cells steady state. We find conditions for Hopf bifurcation of the positive steady state, leading to periodic solutions, sequences of period doubling bifurcations and appearance of chaos. Further, chaos and periodic behavior alternate. Our results are consistent with some clinical and experimental observations.

1. **Introduction.** Reports of an increased incidence of *Pneumocystis carinii pneumonia* (PCP) and *Kaposi's sarcoma* (KS) in New York City and Los Angeles in 1981 heralded the AIDS epidemic. Today, over 60 million people worldwide have been infected with HIV—more than 80% of whom live in developing countries. Although most of these people will die of infectious disease complications, cancers are also taking their toll. Among these, KS is the most common neoplasm that occurs in patients with AIDS (AIDS-KS).

Cancer remains a significant burden for HIV-1 infected individuals. Most of these are virus-associated cancers. Intermediate and high-grade *non-Hodgkin's lymphomas* (NHL) with a B-cell phenotype are AIDS-defining illnesses. The incidence of systemic NHL is over 100 times increased, primary central nervous system NHL is over 3000 times increased, and *Hodgkin's* disease is approximately 10 times increased

2000 *Mathematics Subject Classification.* 92C60.

Key words and phrases. HIV-1 infection, cancer, steady state, stability, Hopf bifurcation, chaos.

in the HIV-infected population. Unusual presentations of NHL and *Hodgkin's* disease are seen in HIV-infected individuals. High-grade histologies are common for both NHL and *Hodgkin's* disease in the HIV setting [1].

Therapists find no viral sequence in the DNA of the cancer cells. So, they think the HIV-1 particle can not by itself engender tumours in an HIV patient [2].

The immune surveillance hypothesis was first raised by Paul Ehrlich in 1909; he proposed that one role of the immune system was to destroy tumours that arise spontaneously on a continued and frequent basis [3, 4]. The discovery of tumour-specific antigens and the ability to prevent tumour development in mice by inducing immunity against such antigens supported this theory [4, 5, 6].

Gaining insight into the epidemiology and mechanisms that underlie AIDS-related cancers can provide us with a better understanding of cancer immunity and viral oncogenesis. How can the combination of immunosuppression and activation of inflammation promote cancer development? Our purpose in this paper is to try to give a glancing analysis using a simple dynamical model.

The use of mathematical models as an aid in understanding features of HIV-1 and virus infection dynamics has been substantial in the past 10 years. Studies [7, 8, 9] have shown that there are two ways for HIV-1 to disseminate in vivo: circulating free viral particles to T cells directly, or through HIV-infected T cells to healthy T cells[10, 11, 12]. Most of these models focus on cell-free virus spread in the bloodstream [13, 14]. But HIV-1 is thought to be active in areas such as the brain and lymph tissues, where 98% of the CD4+ T cells in vivo are found [15]. According to the literature [10, 16], the cell-to-cell mechanism of HIV-1 transfer has been estimated to be much more important and also more efficient than infection by free virus particles in these compartments. Therefore, a model concerning the cell-to-cell spread of HIV-1 is relevant, since understanding the dynamics of the HIV infection within lymphatic tissues is vital to uncovering information regarding cellular infection and viral production. Culshaw and his colleagues [17] presented a model of cell-to-cell spread of HIV-1 in tissue cultures. In [18], Lou and Ma also considered the cell-to-cell spread mechanism, but they mostly focused on two important activities during HIV-1 infection: the impact of the CD8+ cell non-cytotoxic anti-viral response (CNAR) and cytotoxic T lymphocyte (CTL) activity on infection by HIV-1.

The model explored here is a cell-to-cell spread of HIV-1 together with cancer cells in tissue cultures (in vitro). There is precedent for studying in vitro cell-to-cell spread of HIV-1 (as well as that of other viruses) [10, 17, 18], since many features are easier to determine experimentally in tissue cultures than in a more complex medium such as the bloodstream. This model is aimed at explaining some quantitative features concerning cancer occurring during HIV-1 infection that are unusual and, in the absence of a model, perplexing.

The basic starting point of this model has three parts. First, the cancer cells are caused by the changes of the normal cell in the individual due to some physical, chemical or biological factor, , for example, a virus such as human papilloma virus (HPV). Under normal conditions, the healthy cells in our body can mutate into cancer cells with probability of 10^{-6}, and some of them can produce cancer under the influence of carcinogens, including viruses. In clinical studies of AIDS-related cancer, we say that the cancer is a single clone mechanism. Second, the cancer cells have some special genes and so they proliferate in a special way which is different from normal cells. Third, the immune system can recognize the difference

between cancer cells and normal cells, so it can survey them and then carry out its killing function. Considering the key position of CD4+ lymphocyte, we use them to represent the immune system in our model. After binding and then killing the cancer cells, the CD4+ lymphocyte can bind with other cancer cells before it is destroyed by them. Of course, the model built here is by no means a comprehensive model of the interaction between HIV-1 and the immune system. Our aim is to investigate the cancer situation in an individual who is invaded by HIV-1.

As we will show, the model has a number of steady states whose existence and stability properties are quite consistent with their biological meanings. Furthermore, under some special situations of the virus and the immune system, some unusual phenomena for HIV-infected individuals can appear—the stable cyclic changes of three kinds of cells: the number of the cancer cells, the healthy cells and the HIV-1 infected cells. Also, a chaos phenomenon can exist under some other conditions. Periodic solutions and chaos appear alternately along with the changing of the bifurcation parameter.

This paper is organized in the following manner: The model is developed in section 2, and the theory results are given in sections 3. The numerical stimulation results can be found in section 4, and the discussion is in section 5.

2. **The model.** We use $C(t)$ to represent the concentration of cancer cells, $T(t)$ to represent the concentration of healthy cells and $I(t)$ to represent the concentration of infected cells. Because of the immune response caused by HIV-1 in tissue culture in vivo, we develop an ODE model as follows:

$$\begin{cases} \dfrac{dC}{dt} &= C(t)\left[r_1\left(1-\frac{C(t)+T(t)+I(t)}{m}\right)-k_1T(t)\right], \\ \dfrac{dT}{dt} &= T(t)\left[r_2\left(1-\frac{C(t)+T(t)+I(t)}{m}\right)-pk_1C(t)-k_2I(t)\right], \\ \dfrac{dI}{dt} &= I(t)\left(k_2T(t)-\mu_I\right). \end{cases} \tag{1}$$

According to the literature [2, 19, 20], the probability that a healthy cell will become a cancer cell is very small, even if there are some factors that urge the transformation. Compared with the uncontrolled proliferation of cancer cells, the number of healthy cells that convert to cancer cells is very small; therefore this will be omitted in our model. We assume that the cancer is caused by just one cell because of gene mutation and use parameter r_1 to represent its uncontrolled proliferation rate. According to the immune surveillance hypothesis, we use k_1 as the immune system's killing rate of cancer cells; m is the effective carrying capacity of the system; r_2 is the intrinsic growth rate of healthy cells; and p represents the losing rate of the immune cells because of its killing the cancer cells. The infection process of infected-to-healthy cells is described by the mass-action term $k_2T(t)I(t)$, where k_2 is the infection rate coefficient that accounts for the overall effects of HIV-1 reproduction, such as contact rate and infectivity. Finally, μ_I represents the whole immune system's killing effect on the infected cells. For simplicity, we assume this to be a constant, in accordance with Culshaw and Ruan and with Lou et al.[17, 18]. Perhaps in a more realistic model this assumption is too simple. All the parameter values above are non-negative.

We assume initial conditions of:

$$C(0) = C_0, \quad T(0) = T_0, \quad I(0) = I_0.$$

When $C_0 = 0$, then $C(t) = 0$, and system (1) is reduced to a simple two-equation system, which is the same as the model of[18] when parameter $c = 0$. We also know that in this case the system can have three steady states: the trivial equilibrium $E_0 = (0, 0)$, the healthy equilibrium $E_1 = (m, 0)$ and the infected equilibrium $E^* = (T^*, I^*)$. E_0 is always unstable. When $\mu_I > mk_2$, E_1 is globally asymptotically stable and E^* does not exist. When $\mu_I < mk_2$, E^* is globally asymptotically stable. In [18], a time delay system was also discussed and a Hopf bifurcation was found.

3. **Existence and stability of the steady states.** The possible steady states of system (1) are as follows: the trivial steady state, $E_0 = (0, 0, 0)$; the cancer steady state, $E_1 = (m, 0, 0)$; the healthy steady state, $E_2 = (0, m, 0)$; the cancer-healthy steady state, $E_3 = (\bar{C}, \bar{T}, 0) = \left(\frac{mr_2}{r_2+p(r_1+mk_1)}, \frac{mr_1p}{r_2+p(r_1+mk_1)}, 0\right)$; the HIV-healthy steady state, $E_4 = (0, \hat{T}, \hat{I}) = \left(0, \frac{\mu_I}{k_2}, \frac{r_2(mk_2-\mu_I)}{k_2(mk_2+r_2)}\right)$; and the cancer-HIV-healthy steady state, $E^* = (C^*, T^*, I^*)$, in which

$$\begin{aligned} C^* &= \frac{mr_1k_2^2 - (r_1k_2 + k_1r_2 + mk_1k_2)\mu_I}{r_1k_2(k_2 - pk_1)}, \\ T^* &= \frac{\mu_I}{k_2}, \\ I^* &= \frac{k_1[pmr_1k_2 - (r_2 + pr_1 + pmk_1)\mu_I]}{r_1k_2(pk_1 - k_2)}. \end{aligned} \tag{2}$$

About the existence and stability of these steady states we have the following results.

Proposition 1. *Let*

$$R_0 = \frac{mk_2}{\mu_I}, \quad R_1 = \frac{r_1}{k_1} \cdot \frac{k_2(R_0 - 1)}{mk_2 + r_2}, \quad \textit{and} \quad R_2 = \frac{pr_1(R_0 - 1)}{r_2 + mpk_1}.$$

1. *E_0 and E_3 always exist and are unstable; E_1 always exists and is locally stable.*
2. *When $R_0 < 1$, E_2 is locally stable, E_4 and E^* do not exist.*
3. *When $R_0 > 1$, E_2 is unstable and E_4 exists.*
   (a) *When $R_1 < 1$, E_4 is locally stable; E^* does not exist or if it exists is unstable.*
   (b) *When $R_1 > 1$, E_4 is unstable.*
      (i) *When $R_2 < 1$, E^* exists;*
      (ii) *Otherwise, E^* does not exist.*

Biological meanings:

$R_0 < 1$ means $mk_2 < \mu_I$. According to the biological meanings of these parameters, E_2 locally stable when $R_0 < 1$ means that the individual will not be infected by HIV, and so the individual will not develop cancer because the immune system's killing ability for HIV (μ_I) remains strong, the infectious ability of HIV (k_2) is two weak, or both. In other words, if we can prevent the individual from being infected by HIV, then occurrence of these AIDS-related cancers are also avoided.

When $R_0 = 1$, $E_2 = E_4$, then $E_2|_{R_0=1} = E_4|_{R_0=1}$. So a bifurcation happens when $R_0 = 1$.

When $R_0 > 1$ (that is, $mk_2 > \mu_I$), E_2 is unstable and E_4 exists.

When $R_1 < 1$ (that is, $\dfrac{k_1}{r_1} > \dfrac{k_2(mk_2 - \mu_I)}{\mu_I(mk_2 + r_2)}$), E_4 is locally stable and E^* does not exist, or E^* is unstable even if it exists. In biology the situation means the individual will be infected by HIV, since the infectiousness of HIV is too strong or the killing ability of the immune system is too weak, but susceptibility to cancer will not arise because the ability of the immune system to kill cancer cells (k_1) is strong enough; or the proliferation rate of the cancer cells (r_1) is too small.

When $R_1 = 1$, $E_4 = E^*$ since $R_1 = 1 \Leftrightarrow mr_1k_2 - r_1\mu_I - mk_1\mu_I = \dfrac{k_1r_2\mu_I}{k_2}$, and a bifurcation takes place.

When $R_1 > 1$, E_4 becomes unstable and E^* exists under

$$R_2 < 1 \left(r_1(R_0 - 1) < \frac{r_2}{p} + mk_1 \right).$$

That means if the uncontrolled proliferation rate of cancer cells (r_1) is not big enough when compared with the intrinsic growth rate of the healthy cells (r_2) and the immune system's kill rate of cancer cells (mpk_1), then a balance exists between the cancer cells and the HIV-infected cells. Under this condition, the infected cancer-HIV steady state exists and also could be locally stable under some conditions. That means the underlying AIDS-related cancers will occur in the HIV-infected individual.

When $R_2 = 1$, $E^* = E_3$, which means $E^*|_{R_2=1} = E_3|_{R_2=1}$.

Now let's discuss the stability of E^*.

The Jacobian matrix of system (1) at $E^*(C^*, T^*, I^*)$ is

$$J|_{E^*} = \begin{pmatrix} -\dfrac{r_1}{m}C^* & -\left(\dfrac{r_1}{m} + k_1\right)C^* & -\dfrac{r_1}{m}C^* \\ -\left(\dfrac{r_2}{m} + pk_1\right)T^* & -\dfrac{r_2}{m}T^* & -\left(\dfrac{r_2}{m} + k_2\right)T^* \\ 0 & k_2I^* & 0 \end{pmatrix}.$$

Then the characteristic values $\lambda_{1,2,3}$ are the roots of the following equation:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{3}$$

where

$$\begin{aligned} a_1 &= \frac{r_1}{m}C^* + \frac{r_2}{m}T^*; \\ a_2 &= k_2\left(\frac{r_2}{m} + k_2\right)T^*I^* - k_1\left(\frac{r_1}{m}p + \frac{r_2}{m} + pk_1\right)C^*T^*; \\ a_3 &= (k_2 - pk_1)\frac{r_1k_2}{m}C^*T^*I^*. \end{aligned} \tag{4}$$

It is obvious that $a_1 > 0$. From the condition of the existence of E^* in Proposition 1 (which implies $k_2 > pk_1$), we know that $a_3 > 0$.

So, the steady state E^* is asymptotically stable if and only if the following inequality (5) is satisfied:

$$a_1a_2 - a_3 > 0. \tag{5}$$

PROPOSITION 2 *When inequality (5) holds, the infected steady state E^* of system (1) is locally stable.*

Now we choose parameter r_1 as the crucial parameter. Let

$$r_1^* = \frac{k_1(r_2 + mk_2)}{k_2(R_0 - 1)}, \qquad r_1^{**} = \frac{r_2 + mpk_1}{p(R_0 - 1)}.$$

If there exists a $r_1^c > 0$, which satisfies

$$r_1^* < r_1^c < r_1^{**},$$

and $a_1(r_1^c)a_2(r_1^c) - a_3(r_1^c) = 0$, then the characteristic equation (3) would become

$$(\lambda + a_1(r_1^c))(\lambda^2 + a_2(r_1^c)) = 0,$$

which has roots $\lambda_1 = -a_1(r_1^c) < 0$ and a pair of purely imaginary roots: $\lambda_{2,3} = \pm i\sqrt{a_2(r_1^c)}$. If the transversality condition

$$\frac{d}{dr_1} Re\lambda_{2,3}|_{r_1 = r_1^c} \neq 0$$

also holds at this situation, then a Hopf bifurcation will occur when r_1 passes through the critical value r_1^c. Now let us first prove the existence of r_1^c.

Define

$$G(r_1) = a_1(r_1)a_2(r_1) - a_3(r_1).$$

It is easy to prove that

$$C^*(r_1^*) = 0, \qquad I^*(r_1^*) = \frac{r_2\mu_I(R_0 - 1)}{k_2(r_2 + mk_2)},$$

and

$$C^*(r_1^{**}) = \frac{r_2\mu_I(R_0 - 1)}{k_2(r_2 + mpk_1)}, \qquad I^*(r_1^{**}) = 0.$$

So we can calculate that

$$G(r_1^*) = a_1(r_1^*)a_2(r_1^*) - a_3(r_1^*) = \frac{r_2^2\mu_I^2}{m^2k_2^2} > 0$$

and

$$G(r_1^{**}) = a_1(r_1^{**})a_2(r_1^{**}) - a_3(r_1^{**}) < 0.$$

From the mean value theorem we can observe that there does exist a r_1^c, which satisfies $r_1^* < r_1^c < r_1^{**}$, such that $G(r_1^c) = a_1(r_1^c)a_2(r_1^c) - a_3(r_1^c) = 0$.

Also, we can calculate that the transversality condition is

$$\frac{dRe\lambda_{2,3}}{dr_1}|_{r_1 = r_1^c} = -\frac{1}{4(a_1^2(r_1) + a_2(r_1))}\frac{d}{dr_1}[(a_1(r_1)a_2(r_1) - a_3(r_1)]|_{r_1 = r_1^c}.$$

So, we only need to prove that

$$\frac{d}{dr_1}[a_1(r_1)a_2(r_1) - a_3(r_1)]|_{r_1 = r_1^c} \neq 0.$$

Let

$$\alpha = \mu_I\left(\frac{r_2}{m} + k_2\right), \qquad \beta = \frac{r_2\mu_I}{mk_2}, \qquad \nu = (k_2 - pk_1)\frac{k_1\mu_I}{mk_2},$$
$$\gamma = \left(\frac{r_2}{m} + pk_1\right)\frac{k_1\mu_I}{k_2}, \qquad \omega = \frac{k_1p\mu_I}{mk_2}.$$

Then

$$\frac{1}{dr_1}[a_1(r_1)a_2(r_1) - a_3(r_1)] = -\frac{1}{dr_1}\left(\frac{\omega r_1 + \gamma}{\alpha} \times \frac{C^*(r_1)}{I^*(r_1)} + \frac{\gamma}{\dfrac{1}{m} + \dfrac{\beta}{r_1C^*(r_1)}}\right).$$

From $(C^*(r_1))' > 0$ and $(I^*(r_1))' < 0$ we get

$$\frac{d}{dr_1}[a_1(r_1)a_2(r_1) - a_3(r_1)]|_{r_1=r_1^c} < 0.$$

So, a Hopf bifurcation exists when r_1 passes through the critical value r_1^c. The periodic orbit appears with the periodic time $P = \frac{2\pi}{\sqrt{a_2(r_1^c)}}$.

Since $E^*|_{r_1=r_1^*} = E_4|_{r_1=r_1^*}$ and $E^*|_{r_1=r_1^{**}} = E_3|_{r_1=r_1^{**}}$, the steady state E^* does not exist when $r_1 < r_1^*$ and E_4 is stable. But with the increase of r_1, E^* separates from E_4 when $R_1 > 1 (\Leftrightarrow r_1 > r_1^*)$ and is stable. With the increase of r_1 to $r_1 = r_1^c$, a Hopf bifurcation occurs. And finally, E^* contracts to E_3 when $R_2 = 1$ ($r_1 = r_1^{**}$), and also becomes unstable.

The biological meaning is clear for parameter r_1. When the uncontrolled proliferate rate of the cancer cells r_1 is small, the cancer situation can not be built and only HIV can survive in the individual. If the rate increases to a critical value, the cancer and HIV virus can coexist at the same time. But if r_1 becomes larger, then the coexistence will be destroyed and the cancer structure will develop soon, possible denoting the AIDS phase in the infected individual.

Similar results can also be obtained for parameters k_1 and k_2.

4. **Numerical simulations.** System 1 has been also studied through numerical simulations using parameter values; these are given in Table 1 in order to describe time-dependent regimes.

From the literature of clinical and mathematical models, parameter values are given in Table 1 with the corresponding references.

r_1 $(/day)$[20]	$k_1(/ml/day)$[22]	m $(/ml)$[23]	r_2 $(/day)$[22]
$0.05 \sim 0.5$	$10^{-5} \sim 10^{-3}$	1500	0.03

k_2 $(/ml/day)$[21]	μ_I $(/day)$[17]	p[20]
$10^{-5} \sim 5 \times 10^{-4}$	0.3	0.1

TABLE 1. Parameter values and correspondig references.

There are three Hopf bifurcation parameters in this system, r_1, k_1 and k_2, but considering the biological meanings of the parameters, we mainly discuss the mathematical behavior changing r_1 and k_1.

First, we fix parameter k_2 and let r_1 and k_1 change, and we also choose the other parameter values as $r_2 = 0.03, k_2 = 5e^{-4}, m = 1500, \mu_I = 0.3, p = 0.1$. Then we can obtain the $r_1 - k_1$ Hopf bifurcation shown in Figure 1. In Figure 1, the *o line* is the boundary line of the existence of E^*. The region under the o line is the existence region for E^*. The $*$ line is the Hopf bifurcation line. The region between the o-line and the $*$ line is the stability region for E^*. The region under the $*$ line is the region of instability for E^*. In the unstable region, an asymptotically stable periodic solution and chaos appear along with the change of the value for parameters r_1 or k_1.

Let us consider what happens to the solutions, and hence to the biological meanings of the results, as r_1 increases. At this condition, $r^* = 0.104, r^{**} = 0.3$, and $r_1^c = 0.1591$. So when $r_1 < r_1^c$, E^* is locally stable, but what happens when $r_1 > r_1^c$? We first describe the results of numerical solutions.

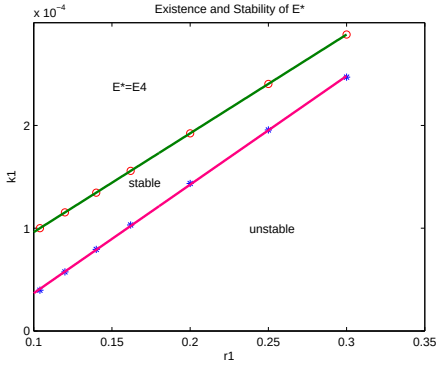

FIGURE 1. The Hopf bifurcation region of parameters r_1 and k_1.

For small values of r_1, the HIV-infected steady state E_4 is stable and the cancer-HIV infected steady state E^* does not exist, which means that cancer susceptibility will not arise when the cancer cell proliferation is not big enough.

As r_1 outpaces r_1^*, E_4 becomes unstable and E^* appears, stable, which means that cancer susceptibly will also arise under the HIV-1 infection.

When r_1 reaches r_1^c, a Hopf bifurcation takes place. E^* becomes unstable for $r_1 > r_1^c$, and a periodic orbit appears, with periodic $P = \frac{2\pi}{\sqrt{a_2(r_1^c)}}$. In the following figures, we first show a period 1 orbit (Figure 2), in addition to the associated fixed point E^*. As r_1 continues to increase, further bifurcations can occur in which such periodic orbits of the flow double their periods repeatedly. So in our simulation we can see the period doubling bifurcations (Figure 3) and then period 4 orbits, and then period 8 orbits and then period 16 and period 32 orbits. Finally, period 64 orbit appear. These accumulate at a point at which transition from periodic to apparently chaotic non-periodic motion—-chaos (Figure 3) occurs. With further increase of r_1, chaos disappears and then period 64 (Figure 4), period 32, period 16, period 8 (Figure 4) and period 4 orbit reappears one by one. After that, period 8 (Figure 5) and period 16 orbit appears for the third time. With the increasing of r_1, chaos appears again (Figure 5) and then a period 4 orbit appears. But after that, chaos appears once more (Figure 6). The numerical solutions show that the orbitally asymptotically stable periodic solution and chaos appear alternately with r_1 increasing. When r_1 increases to r_1^{**}, E^* does not exist and only E_1 is stable, which means that the cancer susceptibility builds is built soon after the HIV infection, which is the situation of some AIDS patients.

Here we report the bifurcation values r_1 ($r_1 = r_1^c + r_1^i$) for the sequences leading to the first appearance of chaos,

$$r_1^1 = 0.019284, \quad r_1^2 = 0.02202005, \quad r_1^3 = 0.022799,$$

$$r_1^4 = 0.0230345, \quad r_1^5 = 0.0230935, \quad r_1^6 = 0.0231059,$$

where $r_1^i, (i = 1, 2, 3, 4, 5, 6)$ is the value at which the orbit of period 2^n undergoes a flip bifurcation, giving birth to an orbit of period 2^{n+1}.

So for

$$\delta = \lim_{n\to\infty} \frac{r_1^n - r_1^{n-1}}{r_1^{n+1} - r_1^n},$$

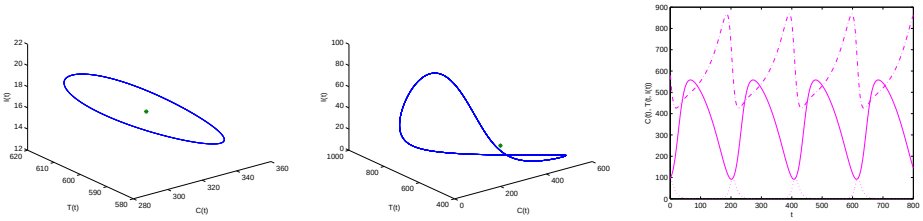

FIGURE 2. When $r_1 = r_1^c + 8 \times 10^{-5}$ and $r_1 = r_1^c + 9.99 \times 10^{-3}$, an orbitally asymptotically stable periodic solution has appeared.

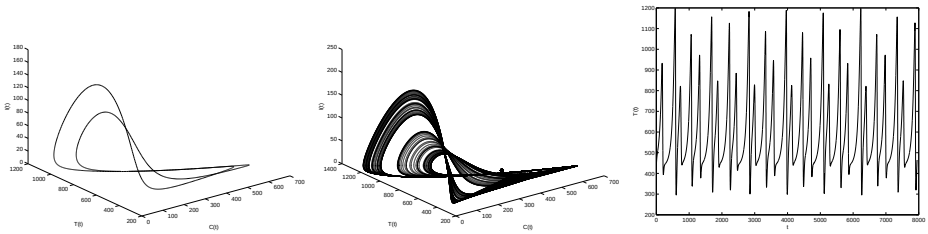

FIGURE 3. When $r_1 = r_1^c + 0.01932$, period 2 orbits have appeared (the left figure); at $r_1 = r_1^c + 0.0235$, chaos has appeared (the middle and right figures).

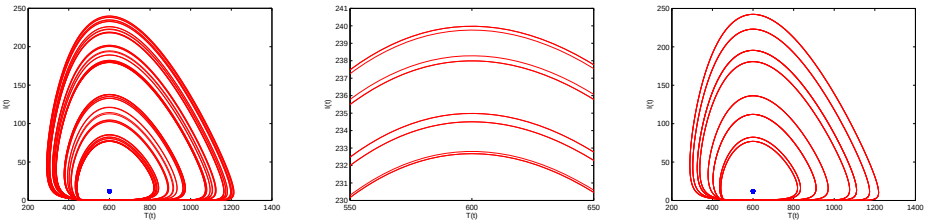

FIGURE 4. When $r_1 = r_1^c + 0.023703$, period 64 orbits appear again (the left figure); the local figure of period 64 orbits (the middle figure); when $r_1 = r_1^c + 0.0238$, period 8 appears again (the right figure).

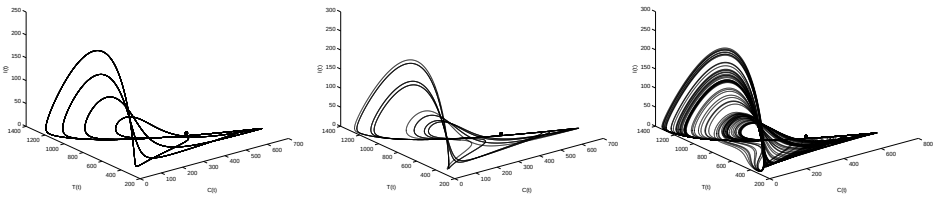

FIGURE 5. When $r_1 = r_1^c + 0.0241$, period 4 orbits appear again (the left figure); when $r_1 = r_1^c + 0.0244$, period 8 orbits appear again (the middle figure); when $r_1 = r_1^c + 0.0251$, chaos appears again (the right figure).

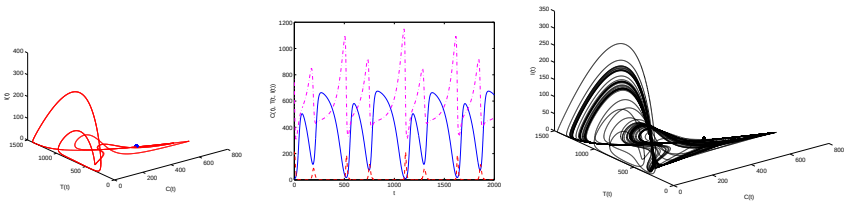

FIGURE 6. When $r_1 = r_1^c + 0.0255$, period 4 orbits appear again (the left and middle figure); when $r_1 = r_1^c + 0.0256$, chaos appears for the third time (the right figure).

the universal number related to appearance of chaos through period doubling (Feigenbaum scenario), we have the sequence of δ_i,

$$\delta_1 \approx 3.5, \quad \delta_2 \approx 3.3, \quad \delta_3 \approx 3.99, \quad \delta_4 \approx 4.76,$$

which is quite close to the universal number, $\delta = 4.669...$, calculated by Feigenbaum for one-dimensional maps [24] and whose first confirmation in the case of a system of ordinary differential equations has been shown in Franceschini and Tebaldi [25].

Now let's look at bifurcation parameter k_1. We fix other parameter values as follows: $r_1 = 0.12, k_2 = 0.0005, r_2 = 0.03, m = 1500, \mu_I = 0.3$ and $p = 0.1$. For these parameters, $k_1^* = 0$, $k_1^{**} = 1.1538 \times 10^{-4}$ and $k_1^c = 0.5746 \times 10^{-4}$. When $k_1 > k_1^c$, E^* is stable, but when k_1 decreases and passes from k_1^c, Hopf bifurcation appears. We find that when k_1 decreases from k_1^c, the topological structure of the orbits change between periodic orbits and chaos for many times: periodic orbits $\rightarrow$ chaos $\rightarrow$ periodic orbits $\rightarrow$ chaos $\rightarrow$ periodic orbits $\rightarrow$ chaos $\rightarrow$ tends to E_1.

We find that k_2 is also a Hopf bifurcation parameter. Choose $r_1 = 0.162, k_1 = 0.0001$, and the other parameter values as before, then $k_2^* = 3.9457 \times 10^{-4}, k_2^c = 4.9385 \times 10^{-4}$. When $k_2 \in [3.9457 \times 10^{-4}, 4.9385 \times 10^{-4}], a1 * a2 - a3 > 0, E*$ is stable. Along with the increase of k_2, E^* becomes unstable, and further bifurcations can also occur in which such periodic points and the corresponding periodic orbits of the flow double their periods repeatedly. This shows that the results discussed above and the appearance of chaos are a general behavior of the system.

5. **Discussion.** The existence of oscillations and chaos in a biological model is not novel. The occurrence of the periodic solutions can explain a special condition about the cancer-developing situation under the immune surveillance against cancer regulation that occurs in the HIV-infected individual. The cancer structure and the HIV concentration will neither be eliminated nor increase continuously. It is a dynamic balance between the increasing of cancer cells and HIV-infected cells and the immune surveillance against cancer regulation.This phenomenon has been found in clinics. The report by Gatti et al.[26] is a clinical record which describes a A stable, cyclically changing phenomenon of the number of cancer cells in an untreated hemophilia patient for several years. Similar situations are also found in HIV-infected individuals. Clinicians found that the numbers of the virus and the CD4+ T cells changed cyclically in some HIV individuals. Chaos phenomena in biological systems have also been found experimentally, for example, the throbs of the ventricular cells in a chicken heart can engender chaos phenomenon. Also, research on the throb of the human heart and the galvanic activity of the human

brain found chaos phenomena [20]. Anderson and May [27] find oscillatory and chaotic fluctuations in a dynamical model of the interaction of HIV with the immune system. In [22], Perelson and his colleagues find oscillatory behavior in their HIV model. Perelson also discusses the biological implications of the parameters needed to obtain oscillations, and then map out the regime in parameter space where oscillations ensue. Periodic solutions have also been found in some other literature about HIV [17, 18], but they are from time-delay dynamic models.

There is some other literature concerning periodic solutions and chaos in dynamic models about biological systems. For example, in [20], the authors discussed the idiotype network about the antibody—the AB model. They found Hopf bifurcations and also alternation between oscillation and chaos. The biological meanings of these phenomena is what we are searching for. The aim of this paper was to help describe such oscillatory phenomena and discuss how chaos appears.

We should note that, although these results are interesting, this model is still a very simple one. Some realistic modifications can be made, such as incorporating a time delay during which the cell is infected but has not yet begun to produce virus. Also we plan to study in a later work a possible explanation for the chaos effect, using some asymptotical analysis to better understand the biological meanings.

Acknowledgments. The authors thank the anonymous referees for their useful comments. This paper was given during the stay of Jie Lou as visiting post- doctor at CIRAM of the University of Bologna and was supported in part (T.R. and C.T.) by fondi MIUR Progetto di interesse nazionale *Problemi matematici non lineari di propagazione e stabilità nei modelli del continuo* Coordinatore T. Ruggeri, by the GNFM-INDAM.

REFERENCES

[1] D. J. Straus, HIV-Associated Lymphomas, *HIV-Associated Lymphomas*, 16(2001) 260-265.
[2] J. A. Levy, HIV and the Pathogenesis of AIDS, ISBN 7-03-007902-7. Springer-Verlag, New York, (1999) 239.
[3] F. M. Burnet, Immunologic surveillance in neoplasia. *Transplant. Rev.* 7(1971).
[4] C. Boshoff and R. Weiss, AIDS-RELATED MALIGNANCIES, *Nature Reviews*, 2(2002) 373-382.
[5] L. Gross, Intradermal immunization of C3H mice against sarcoma that originated in an animal of the same line, *Cancer Res.* 3(1943) 326.
[6] G. Klein and E. Klein, Genetic studies of the relationship of tumour-host cells. *Nature* 178(1956) 1389.
[7] M. P. Cranage, Macaques infected with live attenuated SIVmac are protected against super-infection via the rectal mucosa, *Virol.* 229 (1997) 143–154.
[8] D. Klatzmann and F. Barre-Sinoussi, Selective tropism of lymphadenopathy-associated virus (LAV) for helper-inducer T-lymphocytes, *Science*. 225(1984) 59-62.
[9] D. Klatzmann and E. Champagne, T-lymphocyte T4 molecule behaves as receptor for human retrovirus LAV, *Nature*, 312(1984) 767-778.
[10] P. Gupta and R. Balachandran, Cell-to-cell transmission of humman immunodeficiency virus type 1 in the presence of azidothymidine and neutralizing antibody, *J. Virol,* 63 (1989) 2361-2365.
[11] M. L. Diegel and P. A. Moran, Regulation of HIV production by blood mononuclear cells from HIV-infected donors II. HIV-1 production depends on T cell-monocyte interaction. AIDS *Res. Hum. Retro.*, 9(1993) 465-473.
[12] R. D. Schrier, Mechanisms of immune activation of human immunodeficiency virus in monocytes/macrophages, *J. Virol*, 67 (1993) 5713-5720.
[13] D. S. Callaway and A.S. Perelson, HIV-1 infection and low steady state viral loads, *Bull. Math. Biol.* 64 (2002) 29-64.

[14] D. E. Kirschner, S. Lenhart and S. Serbin, Optimal control of the chemotherapy of HIV, *J. Math. Biol.* 35 (1997) 775-792.
[15] Y. Rosenberg and G. Janossy, The importance of lymphocyte trafficking in regulating blood lymphocyte levels during HIV and SIV infections, *Seminars in Immunol*, 11(1999) 139-154.
[16] R. Pearce-Pratt and D. M. Phillips, Studies of adhesion of lymphocytic cells: Implications for sexual transmission of HIV, *Biol. Repro.*, 48(1993) 431-435.
[17] R.V. Culshaw and S. Ruan, A delay-differential equation model of HIV infection of CD4+ T cells, *Math. Bios.* 165(2000) 27-39.
[18] J. Lou and Z. Ma, The impact of the CD8+ cell non-cytotoxic antiviral response (CNAR) and cytotoxic T lymphocyte (CTL) activity in a cell-to-cell spread model for HIV-1 with a time delay, *Journal of Biological Systems*, 12(1)(2004) 73-90.
[19] R. Lefever and T. Erneux, On the growth of cellulare tissues under constant and fluctuating environmental conditions, *Nonlinear Electrodynamics in Biological Systems*, (1984)287.
[20] A. S. Qi, and Y. Du, The nonlinear medels for immunity, *Shanghai Scientific and Technological Education Publishing House*, 1998.
[21] J. L. Spouge, R. I. Shrager and D. S. Dimitrov, HIV-1 infection kinetics in tissue cultures, *Math. Biosci.*, 138(1996) 1–22.
[22] A. S. Perelson, D. E. Kirschner and R. D. Boer, Dynamics of HIV infection of CD4+ T cells, *Mathe.Bios.*, 114(1993) 81-125.
[23] S. P. Layne and M. J. Merges, HIV requires multiple gp120 molecules for CD4-mediated infection, *Nature* 346(1990) 277-279.
[24] M. J. Feigenbaum, Quantitative universality for a class of nonlinear transformations. *J. Statist. Phys.*, 19(1978), no. 1, 25-52.
[25] V. Franceschini and C. Tebaldi, Sequences of infinite bifurcations and turbulence in a five-mode truncation of the Navier-Stokes equations. *J. Statist. Phys.*, 21(1979), no. 6, 707-726.
[26] A. R. Gatti, W. W. Robinson, A. S. Deinare, M. Nesbit, J.J. McCullough, M.Ballow and A.R.Good, *Blood*, 41(1973) 771.
[27] R. M. Anderson and R. M. May, Complex dynamical behavior in the interaction between HIV and the immune system, in *Cell to Cell Signalling: From Experiments to Theoretical Models*, A.Goldbeter, Ed., Academic, New York, (1989) 335-349.

Received on September 15, 2005. Accepted on January 17, 2006.

E-mail address: jie.lou@126.com
E-mail address: ruggeri@ciram.unibo.it
E-mail address: claudio.tebaldi@polito.it