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Hopf Bifurcation and Chaos in a model for HTLV-I infection of $CD4^+$ T- cells

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Abstract. This paper studies the dynamic behaviours of a mathematical model for HTLV-I infection by using bifurcation theory. In fact we are considering Hopf bifurcation of system, because it plays an important role to indicate the disease can return to a steady state, leading to periodic solutions and maybe appearance of chaos as parameter varies. Further, chaos and periodic behaviour alternate.
We know that human T-cell Lymphotropic virus type I (HTLV-I) primarily infects $CD4^+$ helper T-cells. HTLV-I transmission can be either horizontal through cell-to-cell contact, or vertical through mitotic division of infected $CD4^+$ cells. It has been observed that HTLV-I infection has a high pro-viral load but a low rate of pro-viral genetic variation. This model is for HTLV-I infection of $CD4^+$ T-cells that incorporates both horizontal and vertical transmission. At the end, by simulation give an example and we see that our results are consistent with some clinical and experimental observations.

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1 Introduction

Human T cell leukemia virus type I (HTLV-I) was first discovered by Japanese researchers in 1977, and it was isolated at the National Cancer Institute in the United States. HTLV-I is the etiologic agent in a progressive human neurologic disease. Ryou Kubota and et. al (2000) and Robert C Gallo (2005) obtained that HTLV-I is associated with two types of diseases: (i) adult T-cell leukemia (ATL) [7, 14] and (ii) a range of subacute or chronic inflammatory diseases that affect chiefly the eye, skeletal muscle, or central nervous system. Also, Olivier Gout and et.al (1990) and Mitsuhiro Osame and et.al (1990) comprehend that the most commonly recognized of the inflammatory conditions is HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [11, 18], a chronic inflammation of the central nervous system that results in weakness or paralysis of the legs. Dominik Wodarz and et.al (1999) found out the approximately 20 to 40 million people are infected by HTLV-I worldwide, mostly in the Caribbean, southern Japan, Central and South America, the Middle East, and equatorial regions of Africa [24]. The majority of HTLV-I infected individuals remain lifelong asymptomatic carriers. Also, Charles R M Bangham (2003) investigated that approximately 0.25 - 3.8 % of infected individuals develop HAM/TSP, and another 2 - 3 % develop ATL [4].
Alan Cann and Irvin Chen declared that the main target for the viral infection is the $CD4^+$ T-lymphocyte population [6]. In molecular biology, $CD4^+$ (cluster of differentiation 4) is a glycoprotein found on the surface of immune cells such as T helper cells, monocytes, macrophages, and dendritic cells. It was discovered in the late 1970s and was originally known as leu-3 and T4 (after the OKT4 monoclonal antibody that reacted with it) before being named CD4 in 1984 by Alain Bernard [5]. Masaharu Isobe and et.al (1986) and M Ali Ansari-Lari and et.al (1996) detected that in humans, the CD4 protein is encoded by the CD4 gene [2, 13]. $CD4^+$ T helper cells are white blood cells that are an essential part of the human immune system.

They are often referred to as CD4 cells, T-helper cells or T4 cells. They are called helper cells because one of their main roles is to send signals to other types of immune cells, including CD8 killer cells. CD4 cells send the signal and CD8 cells destroy and kill the infection or virus. If CD4 cells become depleted, for example in untreated HIV infection, or following immune suppression prior to a transplant, the body is left vulnerable to a wide range of infections that it would otherwise have been able to fight.

Kai W Wucherpfennig (1992) attain to unlike the HIV which can break free from host cells and infect other T cells, cell-free HTLV-I does not trigger infection [26]. Cell-to-cell contact is normally required to transmit the infection among $CD4^+$ T cells. Infection also spreads vertically through mitosis of $CD4^+$ T cells that harbour HTLV-I pro-virus.

Horacio Gomez-Acevedo, Michael Y Li in 2005 [10] proposed to model the HTLV-I infection of $CD4^+$ T cells, and considered the backward bifurcation in a feasible region for their system. Also, they explained that the multiple stable equilibria exist for an open set of parameter values. In this mathematical model for the infection of $CD4^+$ T cells by HTLV-I based on two-step process theory of both horizontal transmission through cell-to-cell contact and vertical transmission through mitotic division of infected T cells. We also assume a fraction σ of the infected cells survive after the immune system attack. Moreover, in this model the innate immunity only was considered which always present for people with healthy immune systems and its primary function is to defend against pathogens before they can establish infections within the host.

In recent years, impaired immune responses in two dimensional immunosuppressive infection models have attracted more and more attention. Mathematical models have been developed to capture the interaction in vivo among HIV [9, 21, 22]. Their model was general and was satisfied the clinical data. In 2015, Gleria and Tang [9, 22] considered the model in order to investigate the stability of the CTL immune response. And Shu et al [21] in 2014 obtained saddle point for model which shows stable and unstable. Note that all the above investigations were on the eigenvalues with the non-zero real part and they didn't consider the zero eigenvalue. Also, we investigated one zero eigenvalue of their general model which is corresponding to the occurance of transcritical bifurcation [20]. Since our concentration was on AIDS in this model, we changed some conditions of

system in 2015, in order to consider a weak immune system. In final, we showed through a simple mathematical model that a sigmoid CTL response can lead to the occurrence of transcritical bifurcation [20]. Since HTLV-I infection and HIV are retro-virus and have somewhat same mathematical models. Therefore, the results for one of them can be remarkable for other.

In this paper, we investigate Hopf bifurcation for model which Horacio Gomez-Acevedo, Michael Y Li in 2005 [10] made. Because of the fact that Hopf bifurcation help us to indicate the steady state condition for system as the parameters are varied. Moreover, we consider the chaotic behaviour(no one consider for this model) which often appear in biological systems. Therefore, we investigate zero and non-zero(hyperbolic) real part of eigenvalue. The paper organise as follows: In section 2, we will explain the mathematical model [10] and also, we will rescale the parameters in order to make the system more easy to find its equilibria. Section 3 is devoted to Hopf bifurcation of system which its computation will be in the Appendix. Section 4, the chaos theory and Lyapunov exponent will be investigated. Section 5, conclusion will be given.

2 Mathematical Model of HTLV-I infection and its Equilibria

Horacio Gomez-Acevedo, Michael Y Li in 2005 [10] considered the following conditions and made a model for HTLV-I infection of $CD4^+$ T cells:

1) They partitioned the T-cell population into uninfected and infected classes. They denoted x(t) the number of uninfected cells at time t and y(t) denoted the number of infected cells at time t.

2) They assumed that the proliferation of T cells is described by $\nu_1 x(t)[1-(x(t)+y(t)))/k]$, where ν_1 is the proliferation constant and k is the level at which mitotic division of $CD4^+$ T cells stops. Infected cells division is assumed to be similar to that of the uninfected cells, and is described by $\nu_2 y(t)[1-(x(t)+y(t))/k]$, with proliferation constant ν_2. The horizontal transmission of HTLV-I is through cell-to-cell contact between infected and uninfected cells that Wodarz et al. (1999) and Nowak and May (2000) [17, 24] assumed to have a bilinear incidence form $\beta x(t)y(t)$, where β

is the transmission coefficient. Charles R M Bangham (2000) declared that newly infected $CD4^+$ T cells face a strong humoral immune response [3].

3) Horacio Gomez-Acevedo, Michael Y Li in 2005 [10] assumed that only a fraction σ of cells newly infected by direct contact escape the immune system attack, and are able to infect other T cells. Here $0 \leq \sigma \leq 1$.

4) They also assumed that the body generates $CD4^+$ T cells at a constant rate λ and newly generated cells are uninfected. The removal rate of uninfected $CD4^+$ T cells is a constant μ_1, and may include the loss due to natural death and activation by a nonHTLV-I antigen. The removal rate for infected cells, μ_2, may include the loss due to natural causes and cell-mediated immune response.

Therefore, they introduced the following model for HTLV-I infection

$$\begin{cases} \dot{x} = \lambda + \nu_1 x(1 - \frac{x+y}{k}) - \mu_1 x - \beta xy \\ \dot{y} = \sigma\beta xy + \nu_2 y(1 - \frac{x+y}{k}) - \mu_2 y \end{cases} \tag{2.1}$$

There are several parameters for system (2.1) which make difficult the analysis of system. Therefore we rescale system in order to reduce parameters and so we apply the variable transform

$$x = \frac{\mu_2 - \nu_2}{\sigma\beta - \frac{\nu_2}{k}}\,\bar{x},\ \ y = \frac{\mu_2 - \nu_2}{\frac{\nu_2}{k}}\,\bar{y},\ \ dt = \frac{1}{\mu_2 - \nu_2}\,d\tau$$

on the system (2.1). We replace $\bar{x}$, $\bar{y}$ and τ with x, y and t, so the system (2.1) is

$$\begin{cases} \frac{d\bar{x}}{d\tau} = a_1 + a_2\bar{x} - a_3\bar{x}^2 - K\bar{x}\bar{y} \\ \frac{d\bar{y}}{d\tau} = \bar{y}(-1 + \bar{x} - \bar{y}) \end{cases} \tag{2.2}$$

where $a_1 = \dfrac{\lambda(\sigma\beta - \frac{\nu_2}{k})}{(\mu_2 - \nu_2)^2}$, $a_2 = \dfrac{\nu_1 - \mu_1}{\mu_2 - \nu_2}$,$a_3 = \frac{\nu_2}{k}(\dfrac{1}{\sigma\beta - \frac{\nu_2}{k}})$ and $K = \dfrac{\nu_1 + \beta k}{\nu_2}$ (The denominators is not zero).

It is easy to see that the system (2.2) has four equilibrium points: $A =$

$(\overline{x}_1, 0)$, $B = (\overline{x}_2, 0)$, $C = (\overline{x}_3, -1 + \overline{x}_3)$ and $D = (\overline{x}_4, -1 + \overline{x}_4)$, where

$$\overline{x}_{1,2} = \frac{-a_2 \pm \sqrt{a_2^2 + 4a_1a_3}}{-2a_3}$$

and

$$\overline{x}_{3,4} = \frac{-(a_2 + K) \pm \sqrt{(a_2 + K)^2 + 4a_1(a_3 - K)}}{-2(a_3 - K)}.$$

3 Hopf Bifurcation of System (2.2)

Hopf bifurcation is the birth of a limit cycle from an equilibrium in dynamical systems generated by ordinary differential equations, when the equilibrium changes stability via a pair of purely imaginary eigenvalues. The bifurcation can be supercritical or subcritical, resulting in stable or unstable (within an invariant two-dimensional manifold) limit cycle, respectively. *We use Hopf bifurcation in bioscience; because when one infected by HTLV-I infection or Leukemia. After that, the patient's body will defend against the infectious by immune system and also by treatment and the disease again will convert to stable state after a couple of years. Now, we call this recurrence equilibrium as Hopf bifurcation. In fact we search Hopf bifurcation of system, because it plays an important role to indicate the disease can return to a steady state condition.*

Theorem 3.1 *Suppose that the system* $\dot{x} = f_\mu(x)$, $x \in \Re^n$, $\mu \in \Re$ *has an equilibrium* (x_0, μ_0) *at which the following properties are satisfied:*

(H1) $D_x f_{\mu_0}(x_0)$ *has a simple pair of pure imaginary eigenvalues and no other eigenvalues with zero real parts. Then (H1) implies that there is a smooth curve of equilibria* $(x(\mu), \mu)$ *with* $x(\mu_0) = x_0$. *The eigenvalues* $\lambda(\mu)$, $\overline{\lambda}(\mu)$ *of* $D_x f_{\mu_0}(x(\mu))$ *which are imaginary at* $\mu = \mu_0$ *vary smoothly with* μ. *If, moreover,*

(H2)

$$\frac{d}{d\mu}(Re\lambda(\mu)) \mid_{\mu=\mu_0} = d \neq 0$$

then there is a unique three-dimensional center manifold passing through

(x_0, μ_0) *in* $\Re^n \times \Re$.
Note that if we have planar system

$$\dot{x} = f_\mu(x, y)$$
$$\dot{y} = g_\mu(x, y)$$

where μ *is a parameter.*
If a fixed point assume to be located at $(x, y) = (0, 0)$ *and the eigenvalues of the linearized system about the fixed point be given by* $\lambda(\mu), \overline{\lambda}(\mu) = \alpha(\mu) \pm i\beta(\mu)$*, the following conditions are satisfied:*

1. $\alpha(0) = 0$ *,* $\beta(0) = \varpi \neq 0$ *, where* $sgn(\varpi) = sgn[(\partial g_\mu/\partial x)|_{\mu=0}(0, 0)]$.
(non-hyperbolicity condition: conjugate pair of imaginary eigenvalues)

2. $\dfrac{d\alpha(\mu)}{d\mu}|_{\mu=0} = d \neq 0$
(transversality condition: the eigenvalues cross the imaginary axis with non-zero speed)

3. $a \neq 0$ *, where*

$a = \frac{1}{16}(f_{xxx} + f_{xyy} + g_{xxy} + g_{yyy}) + \frac{1}{16\varpi}(f_{xy}(f_{xx} + f_{yy}) - g_{xy}(g_{xx} + g_{yy}) - f_{xx}g_{xx} + f_{yy}g_{yy})$,
with $f_{xy} = (\partial^2 f_\mu/\partial_x \partial_y)|_{\mu=0}(0, 0)$*, etc.*
(genericity condition)

Then a unique curve of periodic solutions bifurcates from the origin into the region $\mu > 0$ *if* $ad < 0$ *or* $\mu < 0$ *if* $ad > 0$*. The origin is a stable fixed point for* $\mu > 0$ *(resp.* $\mu < 0$*) and an unstable fixed point for* $\mu < 0$ *(resp.* $\mu > 0$*) if* $d < 0$ *(resp.* $d > 0$*) whilst the periodic solutions are stable (resp. unstable) if the origin is unstable (resp. stable) on the side of* $\mu = 0$ *where the periodic solutions exist. The amplitude of the periodic orbits grows like* $\sqrt{|\mu|}$ *whilst their periods tend to* $2\pi/|\varpi|$ *as* $|\mu|$ *tends to zero.*

Proof. See [12, 16] ■

Note that, we use the above theorem for equilibrium ($\overline{x}_{3,4} > 1$) in system (2.2). The computation related to region of Hopf bifurcation are in Appendix as Equation (A.4). It means that if we choose the values of parameters as

they satisfy in equation (A.4), then the system (2.2) is in region of Hopf bifurcation and it satisfies in theorem 1 (Hopf bifurcation Theorem) and it has periodic solutions as bifurcation parameter varies. Therefore we apply the equation (A.4) in order to simulate system and discuss about the theoretical results that these assumptions lead to the following system:

$$\begin{cases} \frac{d\bar{x}}{d\tau} = -3 + 2\bar{x} + 1/3\bar{x}^2 - 1\bar{x}\bar{y} \\ \frac{d\bar{y}}{d\tau} = \bar{y}(-1 + \bar{x} - \bar{y}) \end{cases} \tag{3.1}$$

The parameters have been simulated as $(a_1, a_2, a_3, K) = (-3, 2, \frac{1}{3}, -1)$ for system (2.2) in regarding to (A.4). Now, we plot following figures for system (3.1) by using MATLAB:

Figure 1: The typical solution that converges to a stable periodic solution with the initial value $(x(0) = 3.1, y(0) = 2.1)$

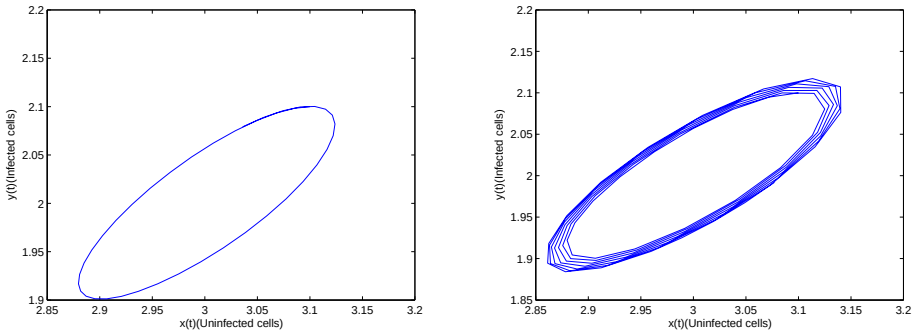
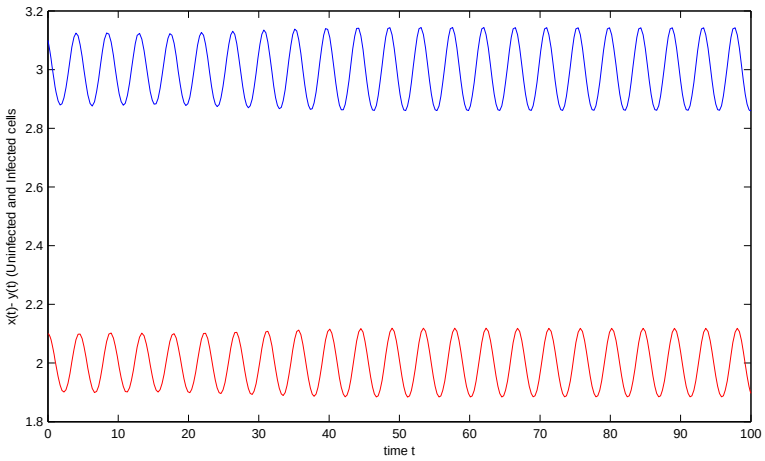


Figure 1. is shown the periodic orbit for system (3.1) which is involved solutions near equilibrium point.

Also, we show the oscillation solutions for $\overline{x}$ and $\overline{y}$ in Fig. 2 that last for any desired length of time. *Hence, there is the coexistence of uninfected and infected cells as well as the innate immunity can either be stable, being approached by damped oscillations, or alternatively can show stable limit cycles.*

Figure 2: Stable Periodic Solution



The occurrence of the periodic solutions can explain a special condition about the infection-developing situation under the innate immunity and It is a dynamic balance between the increasing of infection cells and the immune cells. Since, developing structure of infection to cancer and the hemophilia will neither be eliminated nor increase continuously. The report by [9] is a clinical record which describes a stable, cyclically changing phenomenon of the number of cancer cells in an untreated hemophilia patient for several years. Our results are similar to their clinical results.

Since the parameters are chosen in region of Hopf bifurcation, so system (3.1) keeps its stable periodic solutions. It means that system (3.1) is not sensitive on initial conditions and solutions are still periodic and they can not destroyed, see Fig.3.

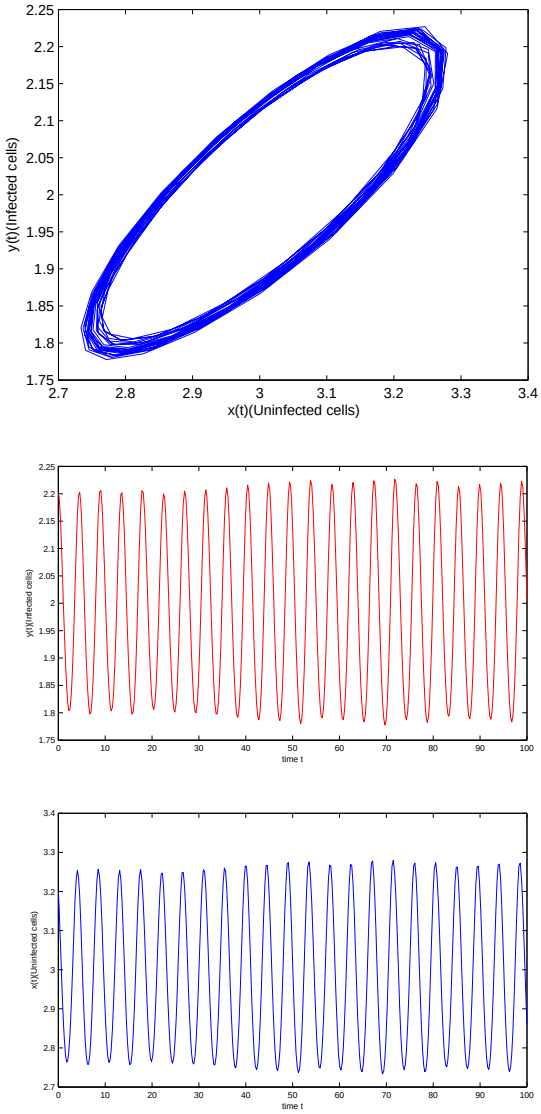


Figure 3: The typical solutions which are not chaotic with the initial value $(x(0) = 3.2, y(0) = 2.2)$

It shows that if one changes the initial conditions of system in Hopf bifurcation region, then solutions also keep periodic orbit.
Now, if we select the parameter values of system (2.2) in out of Hopf bifurcation region; then we can see the chaotic pattern.
Therefore, we will investigate this property and its conditions in the next section.

4 Chaos of System (2.2)

First, we explain the theory of chaos.

The irregular and unpredictable time evolution of many non-linear systems has been called chaos. Chaos occurs in many non-linear systems. Main characteristic of chaos is that system does not repeat its past behaviour. In spite of their irregularity, chaotic dynamical systems follow deterministic equations. The unique characteristic of chaotic systems is dependence on the initial conditions sensitively. Slightly different initial conditions result in very different orbits. But in non-chaotic systems, these differences result in nearly same orbits. In continuous time systems, chaos may occur in systems having at least three independent dynamical variables (Here, we consider one parameter as an independent variable, for example: $\dot{K} = 0$), also system must be non-linear. These are necessary conditions for detecting chaos in continuous time systems. If system has sensitivity to initial conditions, then we say that system is chaotic. After all of these, the exact definition of chaos is that: A chaotic system is a deterministic system that exhibits random and unpredictable behaviour. The defining feature of chaotic system is their sensitive dependence on initial conditions.
Therefore, these initial conditions play an important role in chaos. Since the initial conditions can never be exact in biological mathematical models, the presence of chaos has serious implications for the accuracy of the models. From our investigations, we can conclude that the model exhibits chaotic behaviour for some parameter values. This may be a part of the explanation why the disease develops so differently in individuals.
The chaos theory was summarised by Edward Lorenz as follows: When the present determines the future, but the approximate present does not approximately determine the future. [1, 23]

There are various methods for detecting chaos. These are:
- Time series,
- Phase portraits,
- Poincare maps,
- Power spectrum,
- Lyapunov exponents,
- Bifurcation diagram.[19]
We apply the Lyapunov exponent for computing chaos in this article.

4.1 Lyapunov Exponent

Lyapunov exponents (or characteristic numbers) were first introduced by Lyapunov [15] in order to study the stability of non-stationary solutions of ordinary differential equations.
The Lyapunov exponents are the numbers that measure the exponential attraction or separation in time of two adjacent orbits in the phase space with close initial conditions. n dimensional system has n Lyapunov exponents. If the system has at least one positive Lyapunov exponent, it indicates the chaos. If the largest Lyapunov exponent is negative then the orbits converge in time and system is insensitive to initial conditions. If it is positive, then the distance between adjacent orbits grows exponentially and system exhibits sensitive dependence on initial conditions, so it is chaotic. The main idea of Lyapunov exponent is below:
Suppose x is a point at time t , and consider a nearby point, say $x + \delta$, where δ is a tiny separation vector of initial length. In numerical studies, one Lyapunov finds as $\delta = \delta_0 e^{\lambda t}$. If $\lambda > 0$, neighbouring trajectories separate exponentially rapid. So positive λ indicates the sensitivity to initial conditions.
Assume an initial condition x_0 is chosen arbitrarily. The Lyapunov exponents are

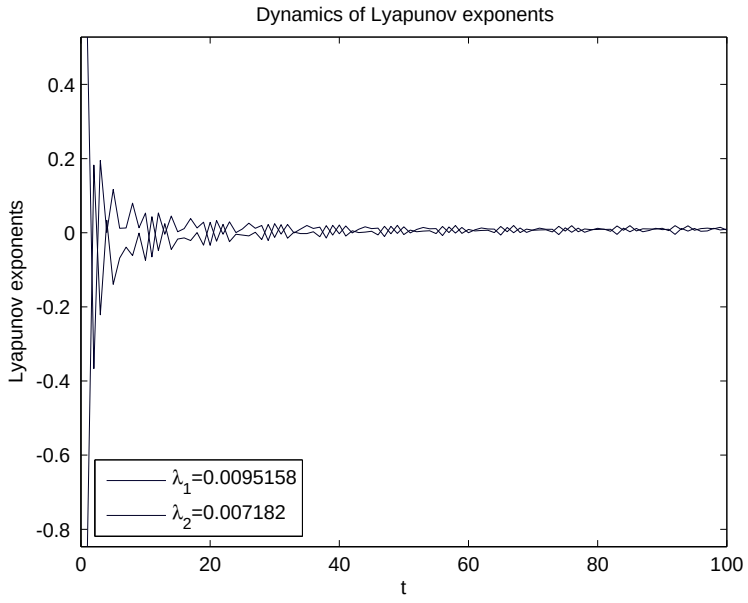
$$\lambda_i = lim_{t\to\infty}\frac{1}{t}ln|m_i(t)| \quad i = 1, 2, \cdots, n$$

which m is the eigenvalues of Jacobian matrix of system [1, 19].

As we mentioned the system may be had chaotic behaviour, it means

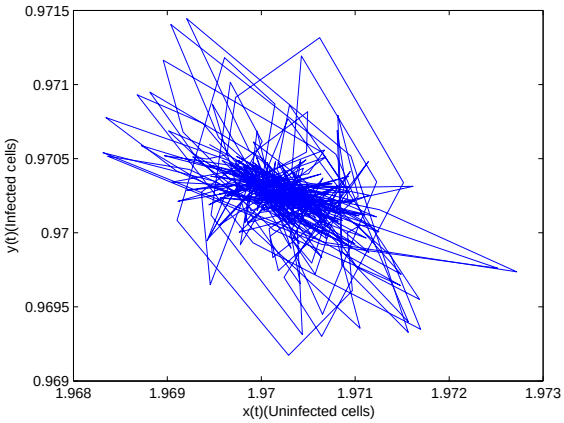
that we can neither manage to find a stable fixed point to be attracted to, nor it is a periodic one. Now, we try to show the chaotic behaviour by Lyapunov exponent. Therefore, we calculate the Lyapunov exponent which should be positive for chaotic behaviour[1]. For this purpose, we use package matds/matlab for system (3.1) in Fig. 4.

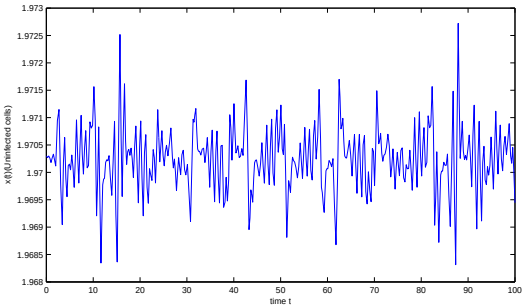
Figure 4: Lyapunov Exponent

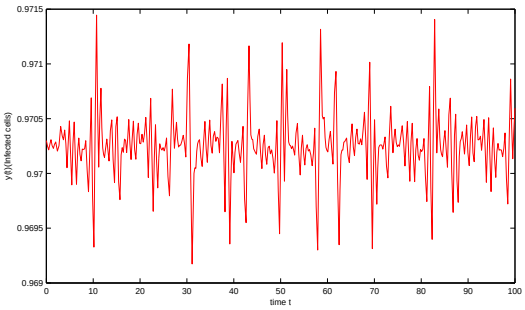


Let choose a point out of Hopf bifurcation region, then we have the chaotic pattern (See Fig. 5). Also, the figures are sensitive dependence on initial conditions for system (3.1). *In fact, Biological systems are dynamic and possess properties that depend on two key elements: initial conditions and the response of the system over time.* It means that if we change the initial conditions then the behaviour of the system is unpredictable.

Figure 5: The chaotic behaviour when $a_1 = 5, a_2 = 2, a_3 = \frac{1}{3}, K = 4$ with the initial value $(1.9703, 0.9703)$







Remark 4.1 *The Fig. 5 displays aperiodic oscillations. This graphical construction implies the chaotic dynamics(at least in some part).*
Since the interaction of body against to cancer is the same, therefore we get the theoretical results from this model which are equivalent to the practical results derivative by wolfram *[25].*
Note that we have analysed Hopf bifurcation and chaos through diagrams and vector fields. The existence of periodic solution can be mentioned that the disease return to a steady state if parameters alter in considerable region which is biologically sound. But if one can choose the parameters in out of Hopf bifurcation region (eigenvalue with non-zero real part) with the different initial conditions, then we have chaotic orbit.
An analysis shows that when the infection through contact with HTLV-I exceeds a certain threshold level, oscillations in the concentration of healthy cells can cross through a Hopf bifurcation region. So, It is caused that the system exhibit chaotic dynamics for realistic parameters.

5 Conclusion

In this paper, we have analysed the dynamic behaviour of HTLV-I infection with innate immunity. Since our system depends on parameters, so bifurcation theory is a good tools for analysing the system. Also Hopf bifurcation helped us to define a region which shows returning the disease to the steady state. In fact we investigated the general conditions for the system (2.1) which goes under Hopf bifurcation. We have applied our results on an example for some values of *clinical parameters* that system will have only one long term motion, while for other slightly different choices or different initial conditions; two or more motions may be possible. Generally, the actual behaviour will be depending on initial conditions(chaotic) and different parameters.

Chaos, in its mathematical sense, refers to irregular behaviour that appears to be random, but is not. The recognition that an irregular behaviour is chaotic, rather than random, signifies that a set of precise rules, rather than chance, governs the irregular behaviour of the system. If the system is sufficiently well understood, the irregular behaviour can be predicted, eliminated or controlled. Chaos theory has been applied very

successfully to a wide variety phenomena exhibiting irregular behaviour for example biology, mathematics, medical. Therefore, the behaviour of system ranges from steady state to oscillation and chaos, that is, from healthy to disease and vice versa and finally in unpredictable conditions for special time.

A Appendices

We compute the Jacobian of system (2.2) at equilibrium points:

$$J = \begin{bmatrix} a_2 - 2a_3\overline{x} - K\overline{y} & -K\overline{x} \\ \overline{y} & -1 + \overline{x} - 2\overline{y} \end{bmatrix}$$

and the associated characteristic equation

$$\lambda^2 - p\lambda + q = 0$$

where

$$p = (a_2 - 1) + (1 - 2a_3)\overline{x} - (2 + K)\overline{y} \tag{A.1}$$

and

$$q = (-a2) + (a_2 + 2a_3)\overline{x} + (-2a_2 + K)\overline{y} + (-2a_3)(\overline{x})^2 + (2K)(\overline{y})^2 + 4a_3\overline{x}\overline{y}$$

Choose p as the bifurcation parameter ($p = \mu$). It follows that from equation (A.1) at point C or D

$$\begin{aligned} a_2 &= (p - K - 1) + (1 + 2a_3 + K)\overline{x}_4 \\ &= (\mu - K - 1) + (1 + 2a_3 + K)\overline{x}_4 \end{aligned}$$

Now, we change coordinates of system (2.2) by letting $\widetilde{x} = \overline{x} - \overline{x}_4$ and $\widetilde{y} = \overline{y} - \overline{y}_4$, then $\overline{x} = \widetilde{x} + \overline{x}_4$, $\overline{y} = \widetilde{y} + \overline{y}_4 = \widetilde{y} + \overline{x}_4 - 1$, $\dot{\widetilde{x}} = \dot{\overline{x}}$ and $\dot{\widetilde{y}} = \dot{\overline{y}}$. Rename $\widetilde{x} = \overline{x}$ and $\widetilde{y} = \overline{y}$, the system is

$$\begin{cases} \dfrac{d\overline{x}}{d\tau} = a_1 + a_2(\overline{x}+\overline{x}_4) - a_3(\overline{x}+\overline{x}_4)^2 - K(\overline{x}+\overline{x}_4)(\overline{y}+\overline{y}_4) \\ \dfrac{d\overline{y}}{d\tau} = (\overline{y}+\overline{y}_4)(-1+(\overline{x}+\overline{x}_4)-(\overline{y}+\overline{y}_4)) \end{cases}$$

where the equilibrium now is (0,0).

The Jacobian matrix for this system at the equilibrium is

$$\begin{aligned} J &= \begin{bmatrix} a_2 - 2a_3(\overline{x}+\overline{x}_4) - K(\overline{y}+\overline{y}_4) & -K(\overline{x}+\overline{x}_4) \\ \overline{y}+\overline{y}_4 & -1+(\overline{x}+\overline{x}_4)-2(\overline{y}+\overline{y}_4) \end{bmatrix} \\ &= \begin{bmatrix} a_2 - 2a_3\overline{x}_4 - K\overline{y}_4 & -K\overline{x}_4 \\ \overline{y}_4 & -1+\overline{x}_4-2\overline{y}_4 \end{bmatrix} \end{aligned}$$

The eigenvalues of this matrix are

$$\alpha(\mu) \pm i\beta(\mu)$$

where

$$\alpha(\mu) = \frac{1}{2}\mu \tag{A.2}$$

and

$$\beta(\mu) = \frac{1}{2}\sqrt{4h-\mu^2} \tag{A.3}$$

where

$$h = (-a_2) + (a_2+2a_3)\overline{x} + (-2a_2+K)\overline{y} + (-2a_3)(\overline{x})^2 + (2K)(\overline{y})^2 + 4a_3\overline{x}\overline{y}$$

For condition 1 of Theorem (3.1), we conclude from equation (A.2) and (A.3) that this condition is satisfy:

$$\alpha(\mu)|_{\mu=0} = 0 \qquad \beta(\mu)|_{\mu=0} = h \neq 0$$

And also, we have $h > 0$ because $\beta(\mu)$ should be real.

The second condition: the derivative of the real part of the eigenvalues

with respect to the parameter μ is

$$\frac{d\alpha(\mu)}{d\mu}|_{\mu=0} = \frac{1}{2} \neq 0.$$

Therefore by Hopf theorem, the system (2.2) under goes Hopf bifurcation.

Now, we evaluate the parameter values of system (2.2) in regard to the following conditions:

(A.4) $\quad 1) \quad \overline{x}_{3,4} > 1, \quad 2) \quad p = \mu = 0, \quad 3) \quad h > 0.$

Also, $a_1 = \dfrac{\lambda(\sigma\beta - \frac{\nu_2}{k})}{(\mu_2 - \nu_2)^2}$, $a_2 = \dfrac{\nu_1 - \mu_1}{\mu_2 - \nu_2}$,$a_3 = \frac{\nu_2}{k}(\dfrac{1}{\sigma\beta - \frac{\nu_2}{k}})$ and $K = \dfrac{\nu_1 + \beta k}{\nu_2}$ and all the parameters $\lambda, \nu_1, \nu_2, k, \beta, \sigma, \mu_1, \mu_2$ are positive, it means that for example if $a_1 < 0$ then $a_3 < 0$.

If we generally select the values of parameters corresponding the above conditions, then the system will show Hopf bifurcation. It means that the system is in region of Hopf and the parameters change in this region.

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