37

Viral diversity in asymptomatic phase of HIV infection

Shingo Iwami [a], Shinji Nakaoka [b]

Department of Mathematical Sciences, Osaka Prefecture University, Japan [a]

Department of Systems Engineering, Shizuoka University, Japan [b]

Abstract

In this paper, we consider the effect of viral diversity on the human immune system with the frequency dependent proliferation rate of CTLs and elimination rate of infected cells by CTLs. In the asymptomatic phase of HIV infection, it is said that there is several thousand viral diversity. Our mathematical model suggests that viral diversity and the frequency dependent rates result in the collapse of immune system. The complex chaotic behavior is observed when two different virus are incorporated.

1   Introduction

Today, there are still many problems on HIV infection which had not been elucidated completely yet, in particular for viral diversity, so long asymptomatic phase and collapse of immune system. In the acute phase of HIV infection, there is few viral diversity. But in the asymptomatic phase, it is said that there is several thousand viral diversity. Therefore we pay attention to viral diversity and the frequency that specific immune cells encounter specific infected cells. Mathematical models for virus dynamics has contributed to elucidate the mechanism of interactions between virus and immune system.

In our study, we propose a mathematical model in which CTL reactions (CTL proliferation and killed rate of infected cells by CTLs) depend on the frequency characterized by the viral diversity which describes the probability that specific CTLs encounter to specific infected cells. Let us define the collapse of immune system by the loss of regulation of immune system. That is, as for the complicated behavior, we consider that the loss of regulation of immune system is serious. The viral diversity and the frequency dependent of CTL reactions are the main subject throughout this paper.

Without viral diversity, we show that the interior equilibrium of one-virus model can be unstable. But our numerical simulations suggest that one-virus model has a stable

limit cycle. Therefore, in this case, we can conclude that, in a point of view of "stable", immune system is regulated if we do not consider viral diversity. However when we incorporated viral diversity (i.e. two-virus model), the frequency due to the viral diversity appeared conspicuously so that our numerical simulations suggested the existence of strange attractors.

Consequently, our mathematical model suggests that viral diversity and the frequency dependent proliferation and elimination of CTLs may lead the collapse of immune system.

2 Model

In this section, we construct a mathematical model which describes viral diversity in the asymptomatic phase of HIV infection. Our model is based on the immune model of infectious disease, which is developed by Nowak and Bangham [8]. This model considers viral diversity, too. There are many immune models elsewhere (see [4], [5], [6], [7], [13], [15]). Nowak et al. incorporated the rate of specific CTLs (Z_j) proliferation in response to specific infected cells (I_j) with the mass action law as cI_jZ_j. However, in their model, there is no interaction among different types of CTLs. In reality, there must be some correlations among different types of specific CTLs (Z_j), which is in turn reflected to the rate of CTL proliferation. In this paper, we assume that the correlation is incorporated as a frequency that the specific CTLs (Z_j) encounter to the specific infected cells (I_j). In the similar manner, we consider that the rate of elimination of specific infected cells (I_j) by the specific CTLs (Z_j) is proportional to this frequency. Our model is given as follows;

$$
\begin{aligned}
T' &= \lambda - dT - \sum_{j=1}^{n} \beta'_j TV_j, \\
I'_j &= \beta'_j TV_j - aI_j - qZ_j \frac{I_j}{T + \sum_{j=1}^{n} I_j}, \\
V'_j &= kaI_j - uV_j, \\
Z'_j &= cZ_j \frac{I_j}{T + \sum_{j=1}^{n} I_j} - \delta Z_j. \qquad (j = 1, 2, ..., n)
\end{aligned}
\tag{1}
$$

This model consists of $3n+1$-variables: T denotes the population sizes of uninfected cells, I_j denotes infected cells with virus particle of type j, V_j denotes the free virus particle of type j, and Z_j denotes the CTLs of type j, respectively. These quantities can either denote the total abundance in a host, or the abundance in a given volume of blood or tissue. All parameters are positive. Remark we assume cell-to-free virus spread of HIV but Rebecca et al. assumed cell-to-cell spread of HIV (see [12]).

The parameter λ is the rate at which new target cells are generated. Uninfected cells,

infected cells, virus and CTLs, die at a rate d, a, u and δ, respectively. Once cells are infected, we assume that they produce k new virus particles during their life, which on average has length $1/a$. Thus, on average, virus is produced at a rate ka. Alternatively, one can view virus as produced in a burst of k particles when infected cell dies; thus producing virus at a per capita rate is ka.

CTL proliferation process in our model is given by $\frac{cZ_jI_j}{T+\sum_{j=1}^{n}I_j}$: The frequency of I_j to all T cells $(T+\sum_{j=1}^{n}I_j)$ is described by $\frac{I_j}{T+\sum_{j=1}^{n}I_j}$. The parameter c is a product of the CTL responsiveness and the number of CTLs encountering to all T cells. The CTL responsiveness describes an average rate at which specific CTL proliferates after it encounters to the specific infected cells. Therefore $\frac{cI_j}{T+\sum_{j=1}^{n}I_j}$ is the rate of CTL proliferation per capita. In the similar manner, the infected cells are killed by CTLs at the rate $\frac{qZ_jI_j}{T+\sum_{j=1}^{n}I_j}$. The parameter q is a product of the rate at which CTLs kill infected cells and the number of CTLs encountering to all T cells. On the other hand, the rate of infected cell proliferation in our model is given by β'_jTV_j, and hence the decay rate of uninfected cells is given by $\sum_{j=1}^{n}\beta'_jTV_j$. The parameter β'_j describes the efficacy of this process, which is the multiplication of the probability at which virus particles find uninfected cells, the rate of virus entry, and the rate of successful infection.

In this model, we emphasize on the specificity for CTLs to encounter with the target cells: we assume that CTLs are activated only if the specific infected cells are encountered to. Without any help of cytokine signal transduction and so on, that is, there is no particular mean of detection, the way of detection of CTLs would be in a random manner. Then the probability that CTLs of type j (Z_j) encounter to the specific target cells (I_j) is given by $\frac{I_j}{T+\sum_{j=1}^{n}I_j}$, reflecting the random search. As the viral diversity increases, it would be expected that the dependence on the frequency of the random search relatively increases. Thus in this model, the effect of viral diversity is reflected in the rate of CTL proliferation and the elimination of infected cells. On the other hand, the healthy T-cell remains as the only resource for all types of virus even if viral diversity increases. As long as the resource is available, virus can increase in frequency independent simple mass action. Note that the form of frequency dependent proliferation rate differs from well-known functional response. CTL proliferation will take the form of Holling type II functional response if the handling time during which CTLs are attaching to infected cells is incorporated (see [1], [2], [3]). In our model, the effect of random search is not represented as a handling time but as the probability that CTLs encounter to the specific infected cells.

We can reduce this model to a simpler form, since the number of free virus particles would change in shorter time-scale than the other variables in Eq.(1) (see [4], [5], [13]). Practically, if the decay rate of free virus u, is much larger than that of the infected

cells a, then we may introduce a good approximation that virus has already been in a steady state (i.e. $V'_j = 0$) and hence $V_j = kaI_j/u$. This leads to the simplified system of differential equations;

$$T' = \lambda - dT - \sum_{j=1}^{n} \beta_j T I_j,$$

$$I'_j = \beta_j T I_j - aI_j - qZ_j \frac{I_j}{T + \sum_{j=1}^{n} I_j}, \tag{2}$$

$$Z'_j = cZ_j \frac{I_j}{T + \sum_{j=1}^{n} I_j} - \delta Z_j. \qquad (j = 1, 2, ..., n)$$

Here we define $\beta_j = ka\beta'_j/u$.

Moreover we can reduce this model to a simple form by scaling Eq.(2) (see [14]). We introduce new variables

$$S = \frac{dT}{\lambda}, \quad H_j = \frac{dI_j}{\lambda}, \quad Y_j = \frac{dZ_j}{\lambda},$$

and Eq.(2) takes the form

$$S' = d - dS - \sum_{j=1}^{n} \frac{\lambda \beta_j}{d} S H_j,$$

$$H'_j = \frac{\lambda \beta_j}{d} S H_j - aH_j - qY_j \frac{H_j}{S + \sum_{j=1}^{n} H_j}, \tag{3}$$

$$Y'_j = cY_j \frac{H_j}{S + \sum_{j=1}^{n} H_j} - \delta Y_j. \qquad (j = 1, 2, ..., n)$$

Finally, we redefine

$$\beta_j \mapsto \frac{\lambda \beta_j}{d^2}, \quad a \mapsto \frac{a}{d}, \quad q \mapsto \frac{q}{d}, \quad c \mapsto \frac{c}{d}, \quad \delta \mapsto \frac{\delta}{d},$$

and also scale time and introduce new time

$$\tau = dt.$$

Since

$$' = \frac{d}{dt} = \frac{d\tau}{dt} \frac{d}{d\tau} = d\frac{d}{d\tau},$$

we obtain the following system;

$$T' = 1 - T - \sum_{j=1}^{n} \beta_j T I_j,$$

$$I'_j = \beta_j T I_j - aI_j - qZ_j \frac{I_j}{T + \sum_{j=1}^{n} I_j}, \tag{4}$$

$$Z'_j = cZ_j \frac{I_j}{T + \sum_{j=1}^{n} I_j} - \delta Z_j, \qquad (j = 1, 2, ..., n)$$

Here we use original notations for the convenience. In the remainder of this paper, we will study Eq.(4). This system describes qualitative dynamics of asymptomatic phase of HIV infection. Note that, as same as system (1), the interactions between specific infected cells and specific CTLs depend on the frequency that specific CTLs encounter to the specific infected cells, but the interactions between uninfected cells and specific infected cells are not frequency dependent.

3 Analysis

In this section, we investigate the stability of equilibria for one-virus model (that is, the model without viral diversity), which is given by the following system of differential equations;

$$T' = 1 - T - \beta_1 T I_1,$$

$$I_1' = \beta_1 T I_1 - a I_1 - \frac{q Z_1 I_1}{T + I_1},$$

$$Z_1' = \frac{c Z_1 I_1}{T + I_1} - \delta Z_1.$$

(5)

This system describes the situation where virus has not mutated yet. Iwasa et al. [4] have proved that an interior equilibrium is globally stable, if the terms associated with immune reactions are given by $c Z_1 I_1$ and $q Z_1 I_1$ instead of $\frac{c Z_1 I_1}{T+I_1}$ and $\frac{q Z_1 I_1}{T+I_1}$ in Eq.(5). However, we show that the interior equilibrium of one-virus model (5) can be unstable. Also our numerical simulations suggest that our model (without viral diversity) has a stable limit cycle. Therefore, in this case, we can conclude that, in a point of view of stability, immune system is regulated (or is not collapsed) if we don't consider viral diversity.

This system describes a situation where virus has not mutated yet and, therefore, describes the dynamics between the acute phase and the early stage of the asymptomatic phase of HIV infection because we don't consider viral diversity.

We will investigate the stability of equilibria. System (5) has three equilibria. The first one is $E_H = (1, 0, 0)$ which represents a state where infected cells are absent.

The second equilibrium E_I represents a state where infected cells are present, while CTLs are absent. Since the Z-component of E_I is 0, the components T^* and I_1^* for $E_I = (T^*, I_1^*, 0)$ are given as follows;

$$T^* = \frac{a}{\beta_1}, \quad I_1^* = \frac{1}{a} - \frac{1}{\beta_1}.$$

If $R_1 > 1$, then E_I exists in $\mathbb{R}_+^3$.

The third equilibrium E_C can be an interior equilibrium, which represents a state in which both infected cells and CTLs are present. Here the interior equilibrium $E_C = (\hat{T}, \hat{I}_1, \hat{Z}_1)$ is represented by the following form;

$$\hat{T} = \frac{-1 + \sqrt{1 + 4\hat{\beta}}}{2\hat{\beta}}, \quad \hat{I}_1 = \frac{\delta}{c - \delta}\hat{T}, \quad \hat{Z}_1 = \frac{c\hat{T}}{q(c - \delta)}(\beta_1\hat{T} - a)$$

where $\hat{\beta} = \delta\beta_1/(c - \delta)$. Here we always assume that c is larger than δ i.e. $c > \delta$ in the following. Note that $Z_1' < 0$ if $c \leq \delta$.

We will consider the local stability of these equilibria. The Jacobian matrix for (5) is;

$$J = \begin{pmatrix} -1 - \beta_1 I_1 & -\beta_1 T & 0 \\ \beta_1 I_1 + \dfrac{qI_1 Z_1}{(T + I_1)^2} & \beta_1 T - a - \dfrac{qZ_1 T}{(T + I_1)^2} & -\dfrac{qI_1}{T + I_1} \\ -\dfrac{cI_1 Z_1}{(T + I_1)^2} & \dfrac{cZ_1 T}{(T + I_1)^2} & \dfrac{cI_1}{T + I_1} - \delta \end{pmatrix}.$$

First, we prove the situation where CTLs are absent in a steady state.

Theorem 3.1. *If $R_1 < 1$, then E_H is LAS. If $1 < R_1 < \dfrac{a\delta}{c - \delta} + 1$, then E_I is LAS and E_H is unstable. Moreover if $R_1 > \dfrac{a\delta}{c - \delta} + 1$, then E_H and E_I are unstable.*

Second, we consider the situation where CTLs are present in a steady state. If we assume $c > \delta$, we can show that the interior equilibrium is LAS under a certain condition.

Theorem 3.2. *Suppose that $c > \delta$. If $\dfrac{a\delta}{c - \delta} + 1 < R_1 < \dfrac{a\delta}{c - \delta} + 1 + \varepsilon$ or $\dfrac{a\delta}{c - \delta} + 1 \ll R_1$, then E_C is LAS. Here ε is a sufficiently small positive constant.*

Next, let us show that E_C becomes unstable under feasible conditions. The characteristic equation is obtained from $\det(p\mathrm{Id} - J_{E_C}) = 0$, where Id is the 3×3-identity matrix. Expanding $\det(p\mathrm{Id} - J_{E_C}) = 0$ gives the characteristic equation $p^3 + a_1 p^2 + a_2 p + a_3 = 0$. Set $s = \delta/c$. Then

$$a_1 = 1 + as + \frac{s^2}{1 - s}(\theta + a),$$

$$a_2 = \delta\theta(1 - s) + s\theta\{-1 + \frac{1 - 2s}{1 - s}(\theta + a)\} + \frac{s}{1 - s}(\theta + a)^2,$$

$$a_3 = \delta\theta(1 - s) + 2s\theta\delta(\theta + a).$$

Note that for sufficiently small s, $1/(1 - s) = 1 + s + O(s^2)$, where $O(s^2)/s \to 0$ as $s \to 0$. Moreover

$$T = \frac{-1 + \sqrt{1 + 4\beta\frac{s}{1 - s}}}{2\beta\frac{s}{1 - s}} = \frac{2}{1 + \sqrt{1 + 4\beta\frac{s}{1 - s}}} = 1 - \beta s + O(s^2).$$

Then $\theta + a = \beta T = \beta - \beta^2 s + O(s^2)$ and $\theta = (\beta - a) - \beta^2 s + O(s^2)$. Direct calculation yields that

$$a_1 = 1 + as + O(s^2),$$
$$a_2 = \delta(\beta - a) + \{\beta^2 + \beta(\beta - a) - (\beta - a) - \beta^2\delta - (\beta - a)\delta\} s + O(s^2),$$
$$a_3 = \delta(\beta - a) + \{2\beta\delta(\beta - a) - (\beta - a)\delta - \beta^2\delta\} s + O(s^2).$$

Hence we have

$$a_1 a_2 - a_3 = \{2(1 - \delta)\beta^2 + (3a\delta - a - 1)\beta + a(1 - a\delta)\} s + O(s^2).$$

For sufficiently small s, the sign of $a_1 a_2 - a_3$ is determined by the sign of the following quadratic function

$$2(1 - \delta)\beta^2 + (3a\delta - a - 1)\beta + a(1 - a\delta)$$

with respect to β.

Theorem 3.3. *Suppose that $\delta > 1$. For sufficiently large β and c, E_C is unstable.*

For instance, assume that $a = \delta > 1$. Then $a_1 a_2 - a_3 < 0$ if $\beta > (3\delta^2 - \delta - 1)/2(\delta - 1)$. Figure 1 illustrates a solution of (5) on $I_1 - Z_1$-plane. The stable limit cycle is observed
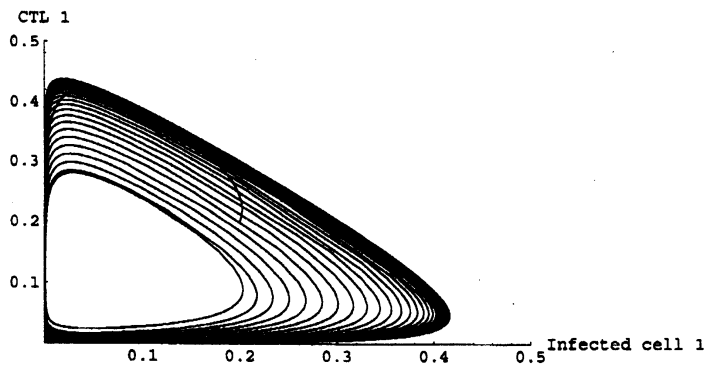

Figure 1: A periodic orbit in $I_1 - Z_1$ phase.

for $\beta = 10$, $a = \delta = 2$ and $c = q = 40$. Note that for relatively large β, a limit cycle generically exists. This implies that an interior equilibrium point of system (5) is likely to be unstable for relatively large β and large c. In other words, if both HIV and immune system are relatively active, then the disease state can be periodic. It is important to note that the solution seems to converge to a stable periodic orbit even when the interior equilibrium point is unstable.

4   Numerical simulations

In this section, we study a two-virus model by simulations. If we do not consider viral diversity (i.e. one-virus model), then the interior equilibrium E_C is LAS or there exists a stable limit cycle. It will be shown for the model with two virus that immune system loses its regulation and the solution behaves chaotically. Two-virus model is given by the following system of differential equations;

$$T' = 1 - T - \beta_1 T I_1 - \beta_2 T I_2,$$

$$I_1' = \beta_1 T I_1 - a I_1 - \frac{q Z_1 I_1}{T + I_1 + I_2},$$

$$I_2' = \beta_2 T I_2 - a I_2 - \frac{q Z_2 I_2}{T + I_1 + I_2}, \tag{6}$$

$$Z_1' = \frac{c Z_1 I_1}{T + I_1 + I_2} - \delta Z_1,$$

$$Z_2' = \frac{c Z_2 I_2}{T + I_1 + I_2} - \delta Z_2.$$

This system describes a situation where virus has already mutated and, therefore, describes the dynamics in the asymptomatic phase of HIV infection. Although several thousand kinds of virus are observed in the asymptomatic phase, here we consider the case where two kinds of virus are present. We carry out a simulation of solutions of (6) with parameters $\beta_1 = 10$, $\beta_2 = 7$, $a = 1.55$, $\delta = 1.5$ and $c = q = 40$.

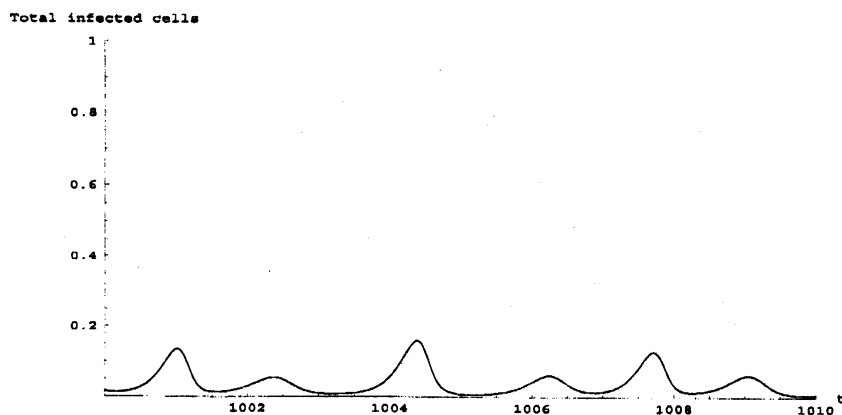Temporal concentration of total infected cells is given by Figure 2. This figure shows

Figure 2: Total infected cells (time is scaled).

that virus load is in a chaotic state and is kept at a low level. Moreover we can choose parameters to make virus load be a periodic state. Since we observe usually discrete clinical data, it may look as if the data is constant. This simulation may warn that virus

load may not be in a steady state but be in a periodic or chaotic state. It is important for us to understand correct virus load in order to make an effective HIV therapeutic strategy.

An example of strange attractors is drawn in Figure 3. Numerical simulations support
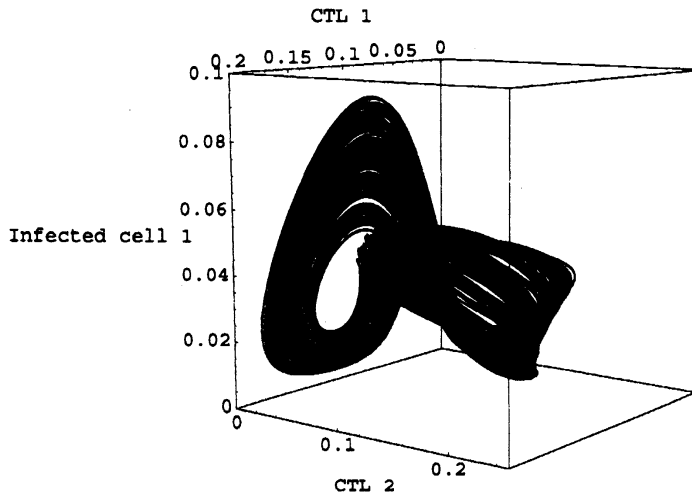

Figure 3: A strange attractor in $Z_1 - Z_2 - I_1$ phase.

that the system exhibits a chaotic behavior and system (6) has a strange attractor in Int $\mathbb{R}^5_+$. If the terms associated with immune response change are given by cZ_iI_i and qZ_iI_i, instead of $\frac{cZ_iI_i}{T+I_1+T_2}$ and $\frac{qZ_iI_i}{T+I_1+T_2}$ ($i = 1,2$), then the interior equilibrium is GAS (see [4]). However our system (6) has strange attractors. Intuitively, the reason why the chaotic behavior occurs is explained as follows: Since immune reactions (CTL proliferation and elimination rate of infected cells by CTLs) depend on the frequency that the specific CTLs encounter to the specific infected cells, initially immune system (Z_1) attacks strongly specific infected cells (I_1) with higher frequency of encountering than the other. Therefore I_1 decreases and the other specific infected cells (I_2) may increase, because the rate of CTL proliferation is proportional with the frequency. Note that CTL proliferation rate, $cZ_2I_2/(T + I_1 + I_2)$, will increase with the decrease of I_1. As a result, the corresponding CTLs (Z_2) increases and Z_1 may decrease. We conclude that this continuous alternative irregular change of the dominant specific infected cells may induce chaotic behaviors.

The relationship between concentrations of infected cells of type 1 (I_1) and CTL of type 1 (Z_1) is characterized in Figure 4. Compared Figure 4 with Figure 1, it is clear that the stability of system is lost by viral diversity. In Figure 1, numerical simulations
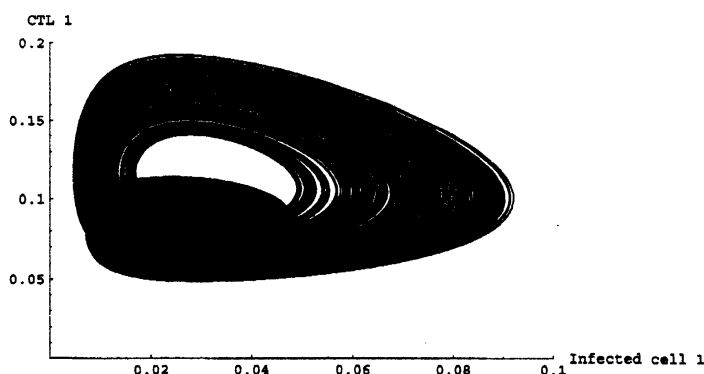
Figure 4: A strange attractor in $I_1 - Z_1$ phase.

support that system has a stable limit cycle. On the other hand, in Figure 4, numerical simulations support that system does not have a stable limit cycle.

The relationship between concentrations of CTL of type 1 (Z_1) and type 2 (Z_2) is characterized in Figure 5. This figure suggests the collapse of immune system in terms
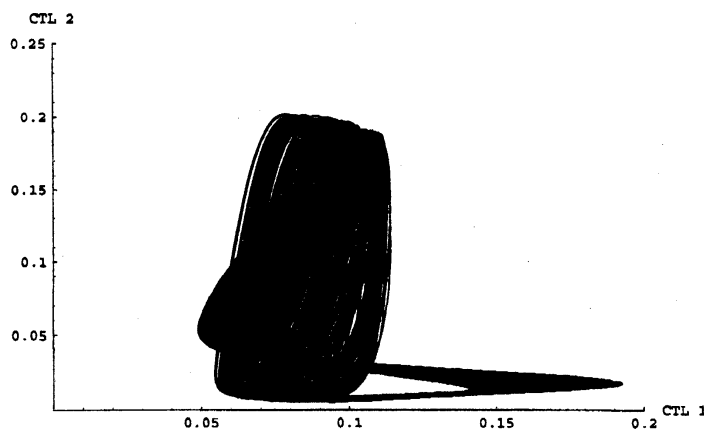

Figure 5: A strange attractor in $Z_1 - Z_2$ phase.

of the loss of regulation. Each concentration of CTLs of type 1 and type 2 varies neither in a steady nor a periodic state, but rather in a chaotic state. Thus CTLs can not be controlled by immune system if the viral diversity is taken into account. In system (5), CTLs can be controlled by immune system in a sense that the solution settles in a steady or a stable limit cycle. On the other hand, in system (6), the immune system has lost its regulation of virus, and the system exhibits a complicated behavior. Therefore viral diversity takes away a regulatory function of immune system.

Consequently, our mathematical model suggests that the effect of viral diversity and the frequency dependence that the specific CTLs encounter to the specific infected cells result in the collapse of immune system and make the behavior of system dynamics be complex.

5 Conclusion

We showed that the interior equilibrium of the one-virus model can become unstable because of the frequency dependence. But our numerical simulation suggested that only a stable limit cycle exists when the equilibrium is unstable. Therefore in this situation, the disease state of patient may be periodic. The interior equilibrium can also become stable so that the disease state may be stable. In both cases, we can conclude that, in our definition of "regularity", immune system remains regulated if we do not consider viral diversity.

On the other hand, our numerical simulations suggested the existence of strange attractors. When we incorporate viral diversity (i.e. two-virus model), the effect of the frequency dependence due to the viral diversity appears conspicuously. We observe continuous alternative immunodominant changes irregularly when the behaviors of two-virus model are chaotic. Therefore in this situation, the disease state of patients is unpredictable and chaotic. Moreover their immune response oscillates irregularly and their disease progression may be faster. Our numerical simulations suggest that viral diversity can cause the collapse of immune system with an emergence of "chaotic behavior".

Finally we conclude this paper with an interesting observation. We will see that system (6) clearly shows a property of destabilization of system as viral diversity increases. For example, we carry out a simulation for the solution of system (6) with parameters $\beta_1 = 10$, $\beta_2 = 8.5$, $a = 1$, $\delta = 1$ and $c = q = 40$. For each positively invariant subsystem of type 1 (system (6) with $I_2 = Z_2 = 0$) and type 2 (system (6) with $I_1 = Z_1 = 0$), Note that each corresponding interior equilibria of the subsystems are LAS. However, Figure 6 shows that system (6) has a periodic attractor in $\text{Int}\mathbb{R}^5_+$. To investigate this property in detail, let us notice that the transversal eigenvalues are given by $\partial \dot{I}_2 / \partial I_2 = \beta_2 \tilde{T}_1 - a$ for the subsystem of type 1 and $\partial \dot{I}_1 / \partial I_1 = \beta_1 \tilde{T}_2 - a$ for the subsystem of type 2. Here $\tilde{T}_1$ and $\tilde{T}_2$ denote the T-component of the interior equilibria of subsystem of type 1 and 2, respectively. In this case, $\beta_2 \tilde{T}_1 - a \approx 6.0153 > 0$ and $\beta_1 \tilde{T}_2 - a \approx 7.44546 > 0$. In other words, both boundary equilibria of entire system (6) are not saturated (see [9]–[11]). Since system (6) is dissipative, periodic attractors can exist even though the interior equilibrium of each subsystem is LAS. Thus stable state of disease can become periodic suddenly as viral diversity increases. This suggests that viral diversity expresses the collapse of immune
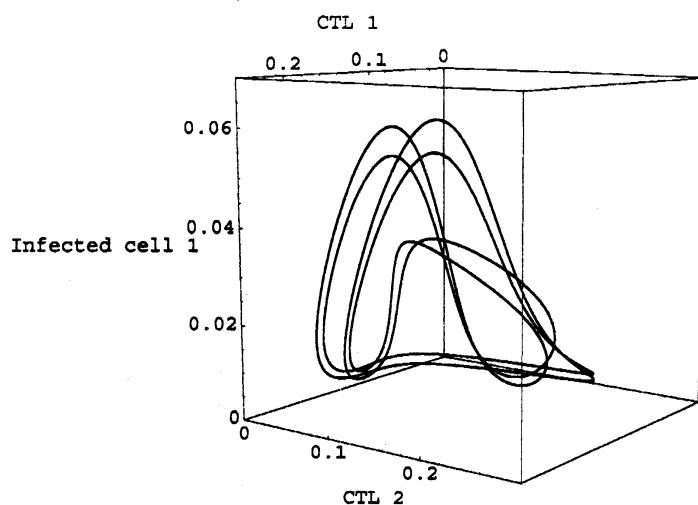
Figure 6: A periodic attractor in $Z_1 - Z_2 - I_1$ phase.

system conspicuously.

Consequently, in both cases, our mathematical model suggests that viral diversity and the frequency dependent proliferation of CTLs and elimination of the infected cells may lead the collapse of immune system.

References

[1] B. M. Adams, H. T. Banks, Hee-Dae Kwon and Hien T. Tran, (2004) Dynamic multidrug therapies for HIV: optimal and STI control approaches, *Mathematical Bioscience And Engineering*, Volume 1, Number 1, 1-21

[2] R. Antia, M. A. Nowak and R. M. Anderson, (1996), Antigenic variation and the within-host dynamics of parasites, *Proc. Natl. Acad. Sci. USA*, **93**, 985-989.

[3] R. J. de Boer, M. C. Boerlijst, (1994), Diversity and virulence thresholds in AIDS, *Proc. Natl. Acad. Sci. USA*, **94**, 544-548.

[4] Y. Iwasa, F. Michor and M. A. Nowak,(2004), Some basic properties of immune selection, *Journal of Theoretical Biology*, 229, 179-188.

[5] Y. Iwasa, F. Michor and M. A. Nowak,(2005), Virus evolution within patients increases pathogenicity, *Journal of Theoretical Biology*, Volume 232, Issue 1, 17-26.

[6] A. Murase, T. Sasaki and T. Kajiwara, (2005), Stability analysis of pathogen-immune interaction dynamics, *Mathematical Biosciences* 51, 247-267.

[7] M. A. Nowak and R. M. May,(2000), Virus Dynamics, Oxford University Press.

[8] M. A. Nowak and C. R. M. Bangham,(1996), Population dynamics of immune responses to persistent viruses, *Science*, 272, 74-79.

[9] M. A. Nowak, R. M. May, R. E. Phillips, S. Rowland-Jones, D. G. Lalloo, S. McAdam, P. Klenerman, B. Koppe, K. Sigmund, C. R. M. Bangham and A. J. McMichael,(1995), Antigenic oscillations and shifting immunodominance in HIV-1 infections, *Nature*, 375, 606-611.

[10] M. A. Nowak, R. M. May and K. Sigmund,(1995), Immune responses against multiple epitopes, *J. theor. Biol.*, 175, 325-353.

[11] M. A. Nowak,(1996), Immune responses against multiple epitopes: a theory for immunodominance and antigenic variation, *Seminars in Virology*, 7, 83-92.

[12] V. Rebecca, Culshaw, Shigui Ruan and G. Webb, (2003), A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay, *J. Math. Biol.* 46, 425-444.

[13] R. R. Regoes, D. Wodarz and M. A. Nowak,(1998), Virus dynamics: the effect of target cell limitation and immune responses on virus evolution, *J theor Biol*, 191, 451-462.

[14] H. L. Smith and P. Waltman (1995) The Theory of The Chemostat. Dynamics of Microbial Competition. Cambridge University Press.

[15] K. Wang, W. Wang and X. Liu, (2006), Viral infection model with periodic lytic immune response, *Chaos, Solitons and Fractals*, 28, 90-99.