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# A time-dependent threshold condition to determine an onset of AIDS

Kouji Harada
Dept. of Knowledge-based Info. Engr.
Toyohasi University of Technology,
1-1, Tenpaku, Toyohashi-shi, Aichi
441-8585, Japan
(E-Mail: harada@tutkie.tut.ac.jp)

Yoshiteru Ishida
Dept. of Knowledge-based Info. Engr.
Toyohasi University of Technology,
1-1, Tenpaku, Toyohashi-shi, Aichi
441-8585, Japan
(E-Mail: ishida@tutkie.tut.ac.jp)

## Abstract

The present study first considers the effect of "noninfectious" HIV-1 due to fatal mutations in HIV-1 population dynamical models, and the analyses of the model reveal AIDS develops when the number of HIV-1 strains, i.e. antigenic diversity is over a "time-dependent" threshold. This result is quite interesting because it suggests a possibility of an onset of AIDS being dynamically determined. This dynamic behavior of the threshold may make the prediction of AIDS development difficult.

## Keywords

HIV-1, Antigenic diversity threshold, noninfectious HIV-1, Double edged sword

## I Introduction

AIDS is an infectious disease with HIV-1 and has still been a threat for mankind. HIV-1's proliferation processes are very subtle. HIV-1 infects its host ($CD4^+$Tcell) through a complimentary binding of a GP-120 molecule on its membrane to a CD4 receptor molecule on the host's membrane. Once inside the host cell, a reverse transcriptase of HIV-1 starts to transcribe HIV-1's RNA genome into cDNA. By referring to the cDNA sequence, a double stranded HIV-1 DNA is elaborated, then it is inserted into the host's DNA. Subsequently genetic machineries of the host cell are manipulated to produce mRNA copies of the viral genome and some functional molecules necessary for the synthesis of new HIV-1 particles. After the enough production of such requisite molecules, new HIV-1 particles are assembled inside the host cell. Finally they bud from the host cell; the host cell will be killed[1].

The present study focuses on an inaccurate transcription of the reverse transcriptase[2] and it leads to put HIV-1 in so-called a "double edged sword" situation. It is known that GP-120 gene is coded in HIV-1 RNA genome; some experimental study reports a transcription accuracy of the reverse transcriptase is very low ($10^{-4}$ mutations/basepairs/replication cycle [3]). Thus, in a transcription process, some mutations must occur on GP-120 gene. In other words, a phenotype of a newly synthesized GP-120 molecule must change (see. Fig.1). GP-120 molecule is a requisite molecule for the infection to the host cell, as well as a target molecule (i.e. antigen) for the immune system. So a phenotypic change of a GP-120 molecule by some mutations may give HIV-1 a possibility to escape a specific immune response; it may deprive an infectious ability from HIV-1. That is "double edged sword" situation. By introducing an "noninfectious" HIV-1, the present model considers "double edged sword" situation[4][5].

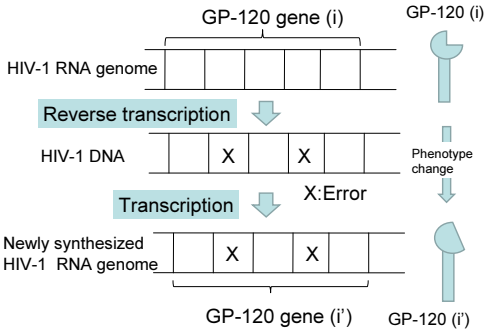


Fig. 1: Mutations on GP-120 gene by a reverse transcriptase

Our study is based on Nowak and May's original work[6]. Our originality is to introduce the noninfectious HIV-1 they did not consider. Their works pro-

posed antigenic diversity threshold theory[6]. The theory suggests there exists a threshold on the diversity of HIV-1 strains and mentions AIDS develops when the number of HIV-1 strains is over the threshold. Meanwhile the present study demonstrates there exists a threshold for an onset of AIDS despite the introduction of the noninfectious HIV-1. However, the threshold has a time dependency. This point is quite different from the Nowak and May's result: their derived threshold is invariant on time[6]. This time dependency reflects the effect of considering the noninfectious HIV-1, in other words, the double edged sword situation.

## II Model

Our proposed model is the following system described as ordinary differential equations:

$$\dot{v}_i = -px_iv_i + \sum_{j=1}^{L} Q_{ij}bv_j \qquad i = 1 \dots M \quad (1)$$

$$\dot{x}_i = kv_i - uvx_i \qquad i = 1 \dots M, \quad (2)$$

$$v = \sum_{i=1}^{M} v_i. \quad (3)$$

Let $v_i$ denote the population size of HIV strain (or mutant) with the antigen (GP-120) $i$ (we simply call it "HIV strain $i$") and let $x_i$ denote the magnitude of the specific immune response against the HIV strain $i$. The differential equation (1) describes a population dynamics of the HIV-1 strain $i$. The first term means an immune response against the antigen $i$ eliminates the HIV-1 strain $i$ at the rate $px_iv_i$. The second term means the HIV-1 strain $j$ mutates into the HIV-1 strain $i$ with a definite mutation probability, $Q_{ij}$. Also an error free replication of HIV-1 strain $i$ is given by $Q_{ii}bv_i$ (Fig. 2).

Our model consists of $N$ different HIV-1 strains by considering the type of antigen ($i$). $M$ strains ($1 \le i \le M$) out of them are survival ones ( holding an ability to infect a host cell); the left strains ($M+1 \le i \le N$) are noninfectious ones (Fig. 2). From the modeling assumptions, the probability $Q_{ij}$ satisfies the following condition:

$$\sum_{i=1}^{N} Q_{ij} = 1 \quad (4)$$

and

$$\sum_{i=1}^{M} Q_{ij} < 1 \quad (5)$$

Meanwhile, the differential equation (2) describes a time evolution of magnitude of an immune response specific for the HIV-1 strain $i$. The first term means an immune response is stimulated at the rate $kv_i$, which is proportional to the abundance of the HIV-1 strain $i$. The second term means the immune response weakens through the decrease of CD4 positive T cells infected by any of HIV-1 strains.

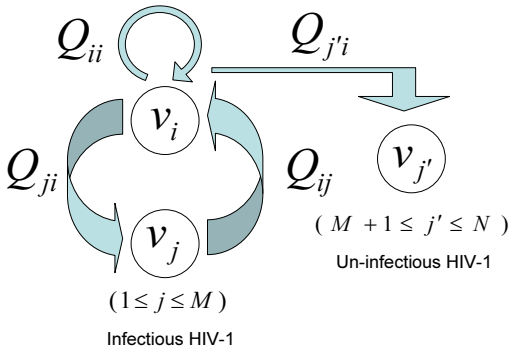


Fig. 2: Schematic view of HIV-1 mutation dynamics

## III Time-dependent threshold condition

As the most fundamental case of the proposed model, this study deals with two HIV-1 strains model, i.e. $M = 2$. This section derives conditional equations controlling an onset of AIDS defined as divergence of the total HIV-1 population.

It assumes the variable $x_i$ converges faster to a steady-state level than the variable $v_i$ does. Thus let $\dot{x}_i$ be zero then we obtain $x_i = \frac{kv_i}{uv}$. Substituting $x_i$ into the Eq.(1), we obtain this equation:

$$\dot{v}_i = \sum_{j=1}^{2} Q_{ij}bv_j - \frac{pk}{uv}v_i^2$$

$$= \phi(\sum_{j=1}^{2} w_{ij}v_j - \frac{v_i^2}{v}), \quad (6)$$

where $w_{ij} = \frac{Q_{ij}b}{\phi}$ and $\phi = \frac{pk}{u}$.

Let $\frac{v_i}{v}$ represent $\bar{v_i}$ and we first examines the time evolution of $\bar{v_1}$. Eq.(6) yields

$$\frac{\dot{v}_i}{v} = \phi(\sum_{j=1}^{2} w_{ij}\bar{v_j} - \bar{v_i}^2) \tag{7}$$

Here, concerning to $\dot{\bar{v_1}}$, the following equation:

$$\dot{\bar{v_1}} = (1-\bar{v_1})\frac{\dot{v_1}}{v} - \bar{v_1}\frac{\dot{v_2}}{v} \tag{8}$$

succeeds. Substituting Eq.(7) into Eq.(8), then

$$\begin{aligned} & \dot{\bar{v_1}} \\ = \ & \phi\left((1-\bar{v_1})(\sum_{j=1}^{2} w_{1j}\bar{v_j} - \bar{v_1}^2) - \bar{v_1}(\sum_{j=1}^{2} w_{2j}\bar{v_j} - \bar{v_2}^2)\right) \\ = \ & \phi F(\bar{v_1}) \end{aligned} \tag{9}$$

is obtained. Here $F(\bar{v_1})$ is defined as a third-order expression of the variable $\bar{v_1}$,

$$\begin{aligned} F(\bar{v_1}) = & (1-\bar{v_1})(w_{11}\bar{v_1} + w_{12}(1-\bar{v_1}) - \bar{v_1}^2) \\ & -\bar{v_1}(w_{21}\bar{v_1} + w_{22}(1-\bar{v_1}) - (1-\bar{v_1})^2). \end{aligned} \tag{10}$$

The time evolution of the variable $\bar{v_1}$ is determined by a shape of the function $F(\bar{v_1})$. The function has the following characters:

- The coefficient of $\bar{v_1}^3$ is positive.
- The value of $F(0)$ is $w_{12}$ $(> 0)$.
- The value of $F(1)$ is $-w_{21}$ $(< 0)$.

These characters suggests there exists $\bar{v_1}^*(0 < \bar{v_1}^* < 1)$ satisfying $F(\bar{v_1}^*)$ is equal to zero. Therefore, the next conditions:

- $F(\bar{v_1}) > 0$ if $0 < \bar{v_1} < \bar{v_1}^*$,
- $F(\bar{v_1}) < 0$ if $\bar{v_1}^* < \bar{v_1} < 1$,

succeed. These conditions imply that the variable $\bar{v_1}$ converges to the value $\bar{v_1}^*$ when the time $t$ goes to the infinite.

Next, we derive a condition on an onset of AIDS defined as divergence of the total HIV-1 population $v(= v_1 + v_2)$.

From Eq.(6), the temporal differentiation of $v$ is described as:

$$\dot{v} = \phi(-\frac{v_1^2 + v_2^2}{v} + \alpha_1 v_1 + \alpha_2 v_2), \tag{11}$$

where $\alpha_i \equiv \sum_{j=1}^{2} w_{ji} (i = 1, 2)$. Furthermore,

$$\begin{aligned} & \frac{d}{dt}(\ln(v)) = \frac{\dot{v}}{v} \\ = \ & \phi(-(\bar{v_1}^2 + \bar{v_2}^2) + \alpha_1\bar{v_1} + \alpha_2\bar{v_2}) \\ = \ & \phi(-(\bar{v_1}^2 + (1-\bar{v_1})^2) + (\alpha_1 - \alpha_2)\bar{v_1} + \alpha_2)) \\ = \ & \phi\left(-S(\bar{v_1}) + H(\bar{v_1})\right) \\ = \ & \phi G(\bar{v_1}), \end{aligned} \tag{12}$$

where $G(\bar{v_1}) \equiv -S(\bar{v_1}) + H(\bar{v_1})$, $H(\bar{v_1}) \equiv (\alpha_1 - \alpha_2)\bar{v_1} + \alpha_2$ and $S(\bar{v_1}) \equiv \bar{v_1}^2 + (1-\bar{v_1})^2$. $S(\bar{v_1})$ is called "Simpson index" which is an inverse measure for "antigenic diversity $D(\bar{v_1})$"; $S(\bar{v_1})$ takes a value between 1/2 and 1.

According to the above discussion, the variable $\bar{v_1}$ converges to $\bar{v_1}^*$ $(0 < \bar{v_1}^* < 1)$; there exist the specific time $T_0$ satisfying $v_1(t) \approx \bar{v_1}^*$ $(t \geq T_0)$. Therefore, after the integration of Eq.(12) from the time $T_0$ to $T(T \gg T_0)$, we obtain

$$\ln\frac{v(T)}{v(T_0)} = \phi\int_{T_0}^{T} G(\bar{v_1})\cdot dt \approx \phi G(\bar{v_1}^*)(T - T_0). \tag{13}$$

From Eq.(13), we can conclude the followings:

1. $\lim_{T\to\infty} v(T) = \infty$ when $G(\bar{v_1}^*) > 0$ i.e. $D(\bar{v_1}^*) > 1/H(\bar{v_1}^*)$,
2. $\lim_{T\to\infty} v(T) = 0$ when $G(\bar{v_1}^*) < 0$ i.e. $D(\bar{v_1}^*) < 1/H(\bar{v_1}^*)$.

The first and the second cases respectively corresponds to conditions of AIDS development and of AIDS suppression. Interestingly, these analyses clarifies there exist the threshold: $1/H(\bar{v_1}^*)$ on the antigenic diversity $D(\bar{v_1})$. It is worth noting that a value of the threshold depends on the time evolution of the variable $\bar{v_1}$. This time-dependency of the threshold is quiet different from Nowak and May's results; their derived threshold is time-independent. This difference is due to the effect of "double edged sword" because if the effect is not considered(i.e. $M = N$), the threshold become a constant value (1).

## IV Conclusions

The present study has first considered the effect of "double edged sword" situation concerning to HIV-1 strategy, and the analyses have revealed AIDS development depends on the "time-dependent" threshold on the antigenic diversity. This result is quite interesting because it suggests a possibility of onset of AIDS being dynamically determined. This dynamic behaviour of the threshold may make the prediction of AIDS development difficult.

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