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Toward Development of a Strategy to Drive HIV-1 into Self-Extinction through the Error Catastrophe

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Abstract: The present study examines a possibility of new AIDS treatment without using anti-HIV-1 drugs to avoid drug resistance. Our idea originated in Eigen [1] is by inducing excess mutations to HIV-1 genome, to drive HIV-1 population to destruction. Namely, we use the high mutation rate of HIV-1 as an underhanded way.

Our study proposes a novel HIV-1 mathematical model considered viral kinetic processes such as mutation, replication, infection and an action of a mutagen to control HIV-1 mutation rate. Through some model simulations by computer it reports to drive HIV-1 population to the error catastrophe by increasing HIV-1 mutation rate.

Keywords: HIV-1, AIDS, Mathematical model, Error catastrophe, Mutagen

1 INTRODUCTION

HIV-1 is the causal virus for AIDS (Acquired Immune Deficiency Syndrome). AIDS treatment mainly depends on drug therapy and now four different types of drugs are used for the therapy. However troublingly all types of drugs easily develop drug resistance if they are used as the sole regimen. In order not to evolve drug resistance, highly active antiretroviral therapy (HAART) based on the administration of at least three different drugs has been executing. However HAART also is somewhat less than perfect in terms of drug adherence because AIDS patients suffer in adverse effects with long-term use. From these reasons, the present study examines a possibility of new AIDS treatment without using drugs. Our idea is by inducing excess mutations to HIV-1 genome, to lead HIV-1 population to destruction. Namely, this study uses the high mutation rate of HIV-1 as an underhanded way.

There were some experimental studies which reported that destruction of a viral population by inducing excess of mutations was achieved. Crotty's group demonstrated inducing excess mutations to poliovirus population by mutagenic action of ribavirin drives poliovirus to error catastrophe, thereby turning a productive infection into an abortive one [2]. Domingo's group reported a similar result on foot-and-mouth disease virus (FMDV) [3].

Meanwhile in the theoretical point of view, quasispecies theory built by Eigen provided a motivation for our study. A viral population structured and maintained by various mutants transiting each other through mutations is called quasispecies [4]. Quasispecies theory suggests when viral mutation rate is crossed a threshold value (called error threshold), viral population formed by the wild type as the primary member changes drastically into a different population dominated by only low fitness mutants This change means that wild type disappears and viral population loses its identity. In terms of HIV-1, it was reported that an estimated HIV-1 mutation rate is near the error threshold value predicted by quasispecies theory, thus HIV-1 barely might keep its identity [5].

Taking the above mentioned background into consideration, the present study proposes a HIV-1 mathematical model considered viral kinetic processes such as mutation, replication, infection and an action of a mutagen to control HIV-1 mutation rate. Through some model simulations by computer it reports it is possible to drive HIV-1 population to the error catastrophe by increasing HIV-1 mutation rate.

2 MODEL

This section proposes a mathematical model to simulate HIV-1 reproduction process. The reproduction process is divided into two phases: (1) replication and mutation process in infected CD4+Tcells and (2) budding and infectious process. First, we introduce a model to simulate HIV-1 replication and mutation process. We consider a quasi-species of HIV-1 population classified into four types: fast or low replication type and viable or defective type referring to [6]. We assume the viable type maintain an ability to permit replication and infection; the defective one

can permit replication but has a deficiency of an ability for infection. In the viable (defective) type, we denote fast replicators to V^* (D^*); slow ones v^* (d^*) where infected state be denoted by an asterisk. The fast replicators have an average of R (greater than one) offspring; slow ones have r (less than one).

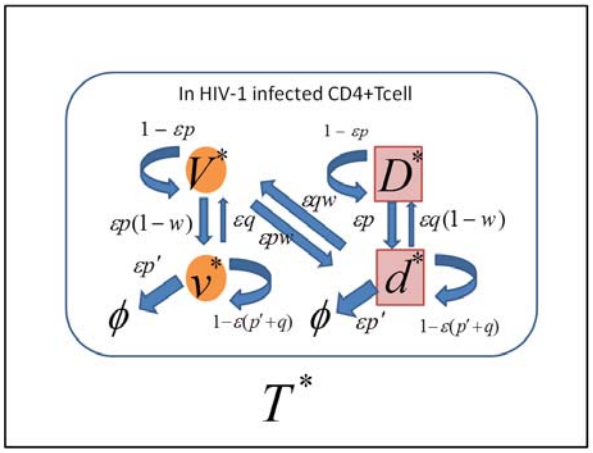

Fig. 1: HIV-1 kinetic processes of viral replication and mutation in HIV-1 infected CD4+T cell.

We assume mutational events occur between the four types. Fig. 1 is a schematic representation of possible mutations between them. This model assumes that (1) a fast replicator mutates a slow one with a mutation rate p; the inverse mutation which is called "backward mutation" occurs with a rate q, whose value is known very small and (2) small ratio (w) of mutated viable HIV-1 population mutates the defective type; the inverse mutation occurs at the same ratio. The replication and mutation process in Fig. 1 is formulated as a population dynamics:

$$\frac{dP_{V^*}}{dt} = F_{V^*}(P_{V^*}, P_{v^*}, P_{d^*}) \equiv R(1-\varepsilon p)P_{V^*} + r\varepsilon qP_{v^*} + r\varepsilon qwP_{d^*}$$

$$\frac{dP_{v^*}}{dt} = F_{v^*}(P_{V^*}, P_{v^*}) \equiv R\varepsilon(1-w)P_{V^*} + r(1-\varepsilon(p'+q))P_{v^*}$$

$$\frac{dP_{D^*}}{dt} = F_{D^*}(P_{D^*}, P_{d^*}) \equiv R(1-\varepsilon p)P_{D^*} + r\varepsilon q(1-w)P_{d^*}$$

$$\frac{dP_{d^*}}{dt} = F_{d^*}(P_{V^*}, P_{d^*}) \equiv R\varepsilon pwP_{V^*} + r(1-\varepsilon(p'+q))P_{d^*}$$

We next formulate HIV-1 infection and budding process represented schematically in Fig. 2. A role model of the process was proposed by Perelson[7] and Wei[8]. Our formulation is based on the role model. T and T^* denote uninfected and infected CD+4 T cells respectively. The four types of "free" HIV-1 are denoted by the previously given symbol without asterisk which means infected state. Uninfected CD+4 T cells are recruited at a birth rate λ and killed at a death rate d; infected ones are killed at δ. Viable and defective HIV-1 is released at a rate γ and s respectively from infected CD4+Tcells.

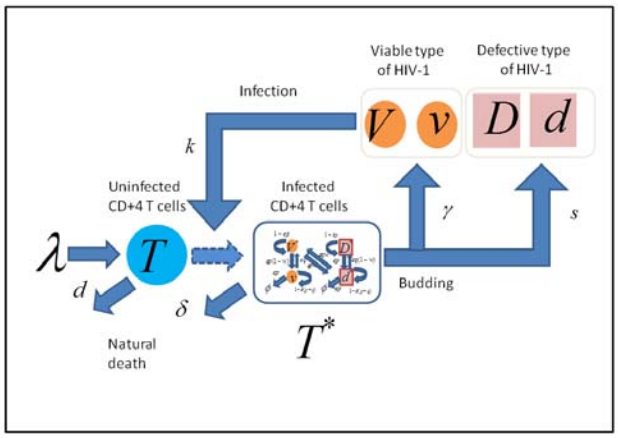

Fig. 2: HIV-1 infection and budding processes

The mutation and replication process of HIV-1 in infected CD4+Tcells and an infection and budding process of free HIV-1 are described by the following equations:

$$\frac{dP_T}{dt} = \lambda - dP_T - k(P_V + P_v)P_T$$

$$\frac{dP_{T^*}}{dt} = k(P_V + P_v)P_T - \delta P_{T^*}$$

$$\frac{dP_{V^*}}{dt} = F_{V^*}(P_{V^*}, P_{v^*}, P_{d^*}) + kvP_T - \delta P_{V^*} - \gamma P_{V^*}$$

$$\frac{dP_{v^*}}{dt} = F_{v^*}(P_{V^*}, P_{v^*}) + kvP_T - \delta P_{T^*} - sP_{d^*}$$

$$\frac{dP_{D^*}}{dt} = F_{D^*}(P_{D^*}, P_{d^*}) - \delta P_{T^*} - sP_{D^*}$$

$$\frac{dP_{d^*}}{dt} = F_{d^*}(P_{V^*}, P_{d^*}) - \delta P_{T^*} - sP_{d^*}$$

$$\frac{dP_V}{dt} = \gamma P_{V^*} - cP_V$$

$$\frac{dP_v}{dt} = \gamma P_{v^*} - cP_v$$

$$\frac{dP_D}{dt} = \gamma P_{D^*} - cP_D$$

$$\frac{dP_d}{dt} = \gamma P_{d^*} - cP_d$$

3 RESULTS AND DISCUSSIONS

3.1 A Mutagen's Action

Our scenario for AIDS treatment is to drive HIV-1 population to destruction due to the increase of the viral mutation rate by a mutagen. We examined feasibility of the scenario in simulations by controlling the parameter ε representing mutagen's action. Fig. 3 shows time series of viral load of free HIV-1 (V) when ε is 0.3, 0.6 and 0.9. The values of parameters except ε are $\lambda = 10^4$ ml/day k=8x10^{-7} ml/day c=13 day^{-1} δ=0.7 day^{-1}, d=0.01 day^{-1}, R=1.3, r=0.1, p=0.5, q=0.09, w=0.2, p'=0.8 [9]. When a mutagen's action is relatively weak (ε=0.3), after a viral load once decreases, it continues to increase and finally leads to developing AIDS; when the mutagen's action is relatively strong (ε=0.9), a viral load continue to decrease slowly and viral eradication is achieved. This case indicates our scenario is feasible. Fig. 3 also clarifies the threshold value of ε of when the downward trend of the viral load changes into the upward trend is 0.8.

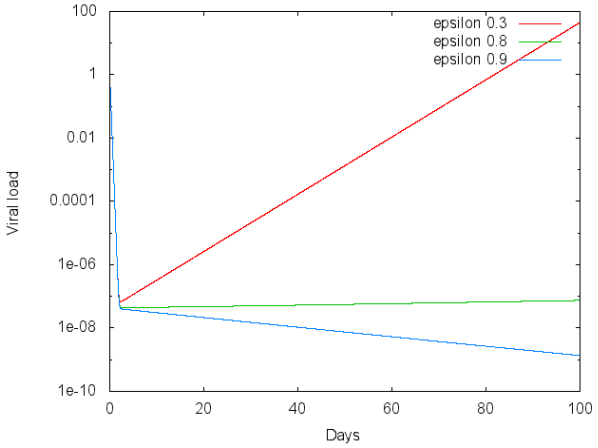

Fig. 3: The changes of time series of viral load over three cases of epsilon value

3.2 The Relationship between the Threshold Value of ε and a Replication Rate, R

We estimated threshold values of ε over the change of the parameter R. Fig. 4 shows the result. The figure indicates the threshold value of ε monotonically increases as parameter R increases. This means that if HIV-1 produces more offspring per replication, destructing HIV-1 population requires intensifying the mutagen's action ε.

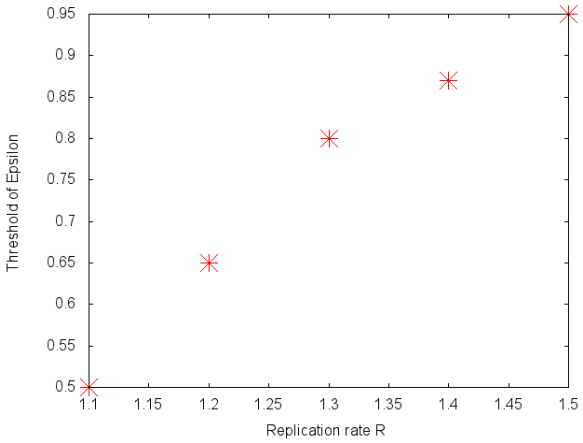

Fig.4: Threshold of the parameter ε versus viral replication rate R

3.3 Mutational Meltdown

The quasi-species theory proposes one scenario of viral extinction that when viral mutation rate is over the threshold value, the wild type disappears from the population and low fitness mutants dominate the population. This type of viral extinction means to lose the identity of the population.

This scenario in the case of our model is interpreted as the following condition:

$$P_V, P_{V^*} = 0;\ P_v, P_{v^*}, P_D, P_{D^*}, P_d, P_{d^*} \neq 0 (t \to +\infty).$$

Now we are studying whether this type of viral extinction occurs.

As another scenario of viral extinction, "mutational meltdown" is known. This scenario mentions all genotypes in the quasi-species disappear simultaneously. In the case of our model, this scenario is described as the followings:

$$P_V, P_{V^*}, P_v, P_{v^*}, P_D, P_{D^*}, P_d, P_{d^*} = 0\ (t \to +\infty).$$

The viral extinction observed in Fig. 3 corresponds to this type of extinction because the sum of four types of HIV-1 population decreases toward zero as displayed in Fig. 5

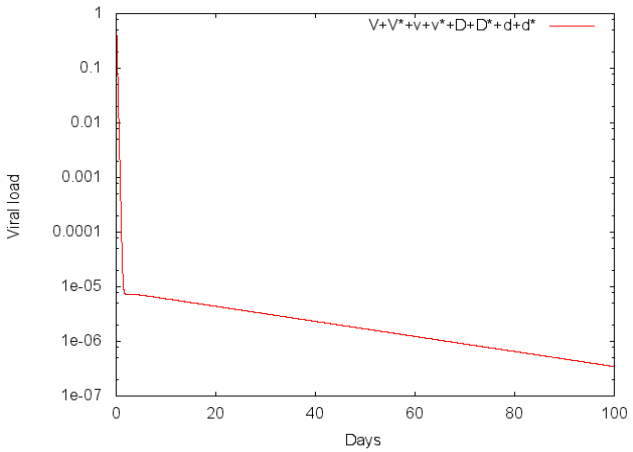

Fig. 5: A time series of the total viral population.

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