A CONTINUOUS STRAIN-SPACE MODEL OF VIRAL EVOLUTION WITHIN A HOST

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Abstract. Viruses rapidly evolve, and HIV in particular is known to be one of the fastest evolving human viruses. It is now commonly accepted that viral evolution is the cause of the intriguing dynamics exhibited during HIV infections and the ultimate success of the virus in its struggle with the immune system. To study viral evolution, we use a simple mathematical model of the within-host dynamics of HIV which incorporates random mutations. In this model, we assume a continuous distribution of viral strains in a one-dimensional phenotype space where random mutations are modelled by diffusion. Numerical simulations show that random mutations combined with competition result in evolution towards higher Darwinian fitness: a stable traveling wave of evolution, moving towards higher levels of fitness, is formed in the phenotype space.

1. Introduction

Compared with many viruses, HIV has unusually high genetic variability within individual hosts and is one of the fastest known evolving entities [7, 22, 23, 62]. This diversity and rapid evolution is the cumulative effect of a combination of several factors. Firstly, HIV replicates remarkably fast; when viral loads for HIV are very high in acute or chronic untreated infection, up to 10^{10}–10^{12} new virions can be generated every day [52, 53]. This is coupled with a high rate of mutation of approximately $3{\cdot}10^{-5}$ per nucleotide base per cycle of replication and recombinogenic properties of reverse transcriptase [39, 56]. Furthermore, HIV has one of the highest recombination rate of all organisms, with about three recombinations per genome per replication cycle on average [37, 29, 73]. This further increases diversity and, eventually, the rate of evolution. These factors in combination result in the generation of many variants of HIV in a host during a single day [56]. The diversity and the ability of HIV to evolve within and among hosts is recognized as a major factor influencing HIV dynamics [71, 40, 62]. The ability to evolve enables the virus to escape from CTL responses [2, 3, 12, 19, 54], leads to development of drug-resistent strains making its treatment extremely difficult [18, 21] and prevents development of an effective vaccine [9, 33, 50].

2010 *Mathematics Subject Classification.* 92D30.
Key words and phrases. Evolution; Mathematical modelling; HIV; Random mutation; Traveling wave.

Certain questions arise when considering intra-host genetic variation and evolution. The first question is what is the driving force behind this evolution? Although it was suggested that genetic drift (that is, stochastic effects) could be responsible for evolution [15], there is strong evidence that the intra-host evolution is mostly driven by positive natural selection [56, 68]. Another question is about the role of immune selection pressure, which could be generated via a number of mechanisms, such as by neutralizing antibodies [3, 9] in this natural selection [56]. It is also not clear how evolution is linked to the development of AIDS [56]. A commonly accepted hypothesis is suggested that increasing diversity leads to an exhaustion of the immune system which, as a result, fails to suppress each emerging variant as well as opportunistic infections [44]. Answering these questions will allow us to better predict the long-term spread of drug resistance and CTL-escape mutations, as well as the likely impact of vaccination [56].

In this notice we mathematically model within-host dynamics of HIV with an aim to address these questions. We use a simple deterministic model of the within-host virus dynamics where a possibility for random mutations is incorporated; simulations with this model demonstrate that random mutations combined with competition result in evolution towards higher Darwinian fitness.

2. Model

The usual approach to the study of viral evolution is to employ multi-strain models; these models were successfully applied for both intra-host [44, 24, 63] and inter-host evolution [6, 5, 11, 13, 17, 38, 51]. Multi-strain models explicitly assume the existence of a discrete [44, 17, 61] or continuous [38, 65, 20, 59] set of viral strains, which form a discrete or continuous strain space (also known as variant space, phenotype space, or fitness space); among other advantages, the concept of strain space allows to introduce a distance between strains [11, 13, 17]. The strains are either predetermined [24, 63, 6, 5], and no new strains can appear in this case, or emergence of new strains is assumed due to random mutations. Random mutations can be modelled by diffusion [38, 65, 20, 59] or its finite-difference equivalent [17, 61] in the strain space; mutations also can be directly described by a stochastic process [44].

Tsimring et al. [65] considered viral evolution using a model where random mutations are described by diffusion in a one-dimensional continuous fitness space. The model exhibits a solution in the form of a pulse-type traveling wave of evolution. An apparent shortcoming of Tsimring et al. model and the result is that the model is not derived from biologically motivated hypotheses or assumptions but is, instead, an equation with the expected dynamics: the model equation, apart from the diffusion term which is used to model random mutations, have no visible biological interpretation. A modification of this model was constructed by

Saldaña et al. [59], who considered a Lotka-Volterra model with distributed competition in a one-dimensional continuous fitness space and with random mutation defined by diffusion.

Sasaki [60], Haraguchi and Sasaki [20], and Sasaki and Haraguchi [61] studied co-evolution of a pathogen and an immune response (antigen drift) within a host using a pathogen-antibodies model with a discrete or continuous one-dimensional strain space. In these studies, all strains were assumed equal and are not interacting in any way; these assumptions made a positive selection or an increase of fitness meaningless in this model framework. This model shows the evolution of antigen variants in the form of a pulse traveling wave in the strain space; on this basis, the authors came to a conclusion that the antigenic drift, by which the pathogen can continuously escape the immune defence, is driven by immune response. We have to note, however, that the pulse wave observed in these studies is a result of superposition of two distinct traveling waves, both of each are of a standard Kolmogorov-Fisher type [32]. The first of these two waves describes the spread of pathogen by diffusion; this wave is followed by the wave of specific immune response, which wipe the pathogen out.

To study inter-host antigenic drift, Lin et al. [38] generalized the classical SIR model by including mutation as a diffusion process in a one-dimensional continuous phenotype space. The major difference between this model and Sasaki's model is that Lin et al. introduced a cross-immunity between the near strains (which is a very important development). This model also exhibits traveling wave solutions. An apparent deficiency of this model is that the strains are of the same level of fitness and that they interact only via cross immunity, and hence there can be no positive selection in this model either. In absence of the cross immunity, the model exhibits a traveling wave of Kolmogorov-Fisher type.

As a basis for this study, we begin with the simplest virus dynamics model that is due to Anderson and May [4], Nowak and May [46] and Wodarz et al. [70]:

$$\begin{aligned} \frac{du(t)}{dt} &= b - \beta u(t)v(t) - du(t), \\ \frac{dv(t)}{dt} &= \beta u(t)v(t) - mv(t). \end{aligned} \tag{1}$$

Here, $u(t)$ and $v(t)$ are populations of healthy (uninfected) and infected target cells, respectively. The uninfected target cells (in the case of HIV these are CD4+ T cells) are assumed to be produced at a constant rate b, and their natural death rate is d; that is, the average life span of a healthy cell is $1/d$. Infected cells die at a rate mv. Susceptible cells are infected by free virus produced by infected cells. In this model, population of free virus is implicitly assumed to be proportional to the population of infected cells. This assumption is justified when the time scale of free virus is much faster than that of the host cells, as in this case the free virus population quickly converges to a quasi-equilibrium level proportional to the infected cell population [27, 69, 66]. Hence, the rate of infection is βuv.

The properties of this model are well-studied (see e.g. [66, 34, 35]). The generic properties of this model are entirely determined by the basic reproduction number of the infected sells $R_0 = b\beta/dm$. The model always has an infection-free equilibrium state Q_0, where $u = b/d$ and $v = 0$. When $R_0 \leq 1$, this equilibrium state is the only equilibrium state of the system and is globally asymptotically stable (that is, for any non-negative initial conditions the system eventually converge to the equilibrium state). If R_0 is larger than 1, then Q_0 losses its stability, and the model has a positive (endemic) globally stable equilibrium state Q^*, where both populations coexist.

Using model (1) as a basis, we assume now that viral strains form a continuous strain space. New strains emerge as a result of random mutations, which in the continuous strain space can be modelled by diffusion. For simplicity we limit our consideration to a 1-dimensional strain space $M = \{s \in [0, \infty)\}$. Then $v(t, s)$ is the distribution of the infected population in the strain space, and the total infected population is $V(t) = \int_0^\infty v(t, s)ds$. In the model (1) framework, a strain is characterized by parameters β and m. For the sake of simplicity, we assume that m is the same for all strains, whereas β is a function of s; we assume in this paper that $\beta(s) = as$ (where $a > 0$). Thus, the basic reproduction number of virus $R_0 = b\beta/dm = bas/dm$ is proportional to s, and s serves as a measure of fitness. These assumptions lead to the following equations:

$$\begin{aligned} \frac{du(t)}{dt} &= b - u(t)\int_0^\infty \beta(s)v(t, s)ds - du(t), \\ \frac{\partial v(t, s)}{\partial t} &= \beta(s)u(t)v(t, s) - mv(t, s) + \mu\frac{\partial^2 v(t, s)}{\partial s^2}. \end{aligned} \tag{2}$$

The natural boundary condition for $v(t, s)$ at $s = +\infty$ is zero. The choice of a condition at $s = 0$ is not obvious; for convenience we use the condition $\frac{\partial v(t,0)}{\partial s} = 0$. The system (2) should be complemented by non-negative initial conditions $u^0 = u(0)$ and $v^0(s) = v(0, s)$.

The variable u is measured in cells$\cdot$mm^{-3}; v is the density of cells in the strain space, and hence it is measured in cells$\cdot$s$^{-1}\cdot$mm^{-3}. The cell production rate b is measured in cells$\cdot$mm$^{-3}\cdot$day^{-1}; m and d are measured in day^{-1}, and β is in cells$^{-1}\cdot$day^{-1}. We postulated above that $\beta \sim s$, and hence s is measured in cells$^{-1}\cdot$day^{-1}, and μ in cells$^{-2}\cdot$day^{-3}.

3. Results

Figures 1 to 4 show results of numerical simulations of equations (2). In this simulations, we use parameter values for patient 2 in [25, 64]: $b = 20$ cells$\cdot$mm$^{-3}\cdot$day^{-1}, $m = 0.8$ day^{-1} and $d = 0.02$ day^{-1}. For convenience of presentation, we take $a = 10^{-3}$; that yields $\beta(s) = s/1000$, and, recalling that for these parameters the infection-free level of uninfected cells is $u_0 = 1000$ cells$\cdot$mm^{-3}, the basic reproduction number $R_0 = \beta u_0/m = s/m$. In simulations we use the

diffusion coefficient μ equal to 10^{-8}, 10^{-7} and 10^{-6} cells^{-2}·day^{-3}; for $\mu \approx 5 \cdot 10^{-7}$, CD4$^+$ T cells level reached 200 cells·mm^{-3} in roughly 10 years, which corresponds to clinical observations [46, 1] and thus mimics the real-life progression of an infection. (However, this does not implies that the real-life coefficient is equal to $5 \cdot 10^{-7}$, as immune response, which is not included in model (2), can have a considerably effect on viral evolution and on all-over disease progression.)

To mimic a real life situation, we assume that the initial virus load is very low and composed of a very narrow band of strains. In Figures 1 to 4 the initial distribution is (see Fig. 3(a)):

$$v(0,s) = \begin{cases} 8(s - 0.9975) & \text{for } 0.9975 \le s < 1.0, \\ 0.02 & \text{for } 1.0 \le s \le 1.005, \\ 8(1.0075 - s) & \text{for } 1.005 < s \le 1.0075, \\ 0 & \text{otherwise.} \end{cases}$$

We have to note, however, that changes in magnitude or dispersion of initial dose has a very small effect on the long term dynamics. Thus, for a relatively wide initial distribution, it is the uppermost non-zero end of the distribution that only matters, whereas the rest of the initial interval relatively quickly disappears. (It is noteworthy, that the same effect was observed by Tsimring *et al.* [65], who misinterpreted this effect and even introduced a cut-off to avoid it.)

Figure 1 shows the distribution of infected cells in the phenotype space for 10 years for $\mu = 10^{-6}$; formation of a pulse traveling wave, which moves towards higher levels of fitness (larger s) in the strain space, is clearly seen in the Figure. This shows that random mutations (which are described by diffusion in the model), in combination with competition for a "resource" (uninfected target cells in this case) leads to viral evolution. This result also shows that immune response is not essential for evolution.

An intriguing feature of evolution in Fig. 1 is that the speed of the traveling wave (speed of evolution) is not constant. (This also can be seen in Figures 2 and 4, which show the dynamics of uninfected and infected populations.) Figures 1 and 2 show that the speed of evolution depends on both the fitness (infectivity in this case) of the strains and the abundance of uninfected target cells: the speed of evolution steadily grows with the growth of the infectivity until the level of the uninfected cells drops below a certain threshold; after this moment evolution slows and its speed remains approximately constant. In Figures 1, where $\mu = 10^{-6}$, this slow-down occurs at about 6.7 years; for smaller μ this change of the dynamics occurs later and is even more evident (see curves for $\mu = 10^{-7}$ and 10^{-8} in Fig. 2).

For relatively low μ (e.g. for $\mu = 10^{-8}$ in Fig. 2), the varying speed of evolution leads to the dynamics which has close qualitative resemblance with the typical progression of HIV infection. In Fig. 2, a relatively short transition period is followed by a longer period of slow evolution, when the level of uninfected CD4$^+$ T cells is decreasing very slowly. This period, which is resembling the asymptomatic

stage of HIV infection, ends with a comparatively fast acceleration of evolution and a fast drop of the uninfected $CD4^+$ T cells level; this can be associated with the abrupt drop of the $CD4^+$ T cells level at the end of the asymptomatic stage and the development of AIDS.

Numerical simulations show that the evolution leads to an increase of viral diversity; Figure 3(b) shows distributions of the infected population in the strain space after 10 years of evolution for $\mu = 10^{-6}$, 10^{-7} and 10^{-8}. However, this increase of diversity is lower than it can be expected. Moreover, distribution after 10 years is almost independent from an initial distribution.

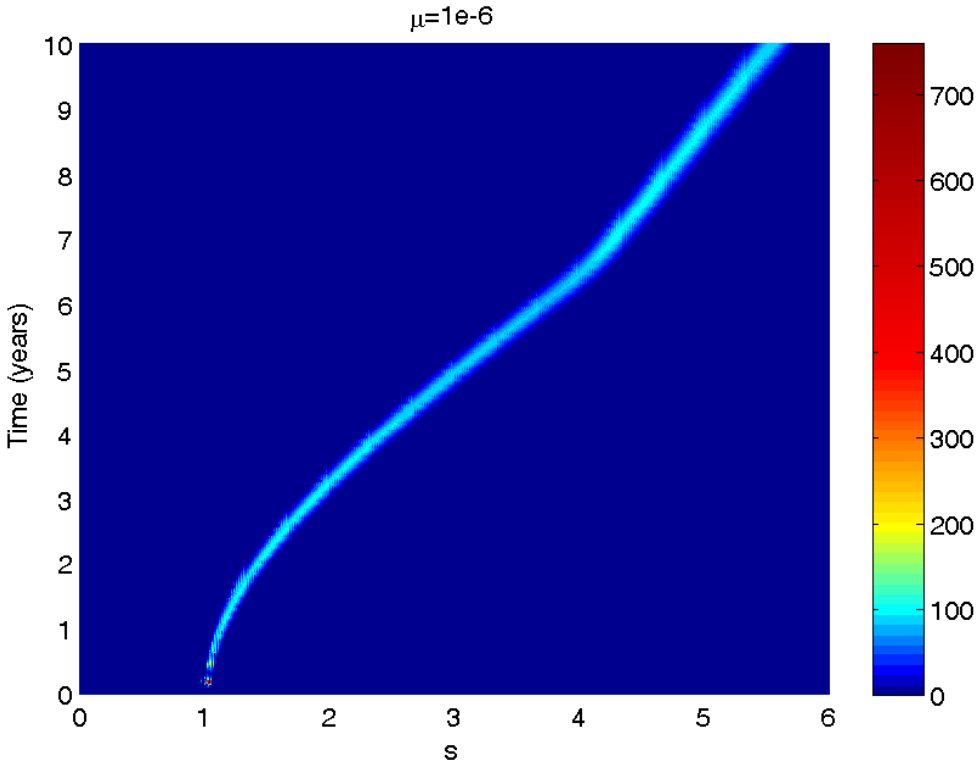


FIGURE 1. Distribution of the infected cells population in the phenotype space for 10 years. Please note formation of a pulse-type traveling wave of evolution and the variable speed of the wave. Here, $b = 20$ cells·mm^{-3}·day^{-1}, $m = 0.8$ day^{-1}, $d = 0.02$ day^{-1}, $a = 10^{-3}$ and $\mu = 10^{-6}$cells^{-2}·day^{-3}.

4. Discussion and Conclusion

The aim of this study was mathematical modelling of within-host evolution of HIV. We suggest and consider a mathematical model of the within-host dynamics of HIV, which is an extension of the Nowak-May model of virus dynamics in vivo,

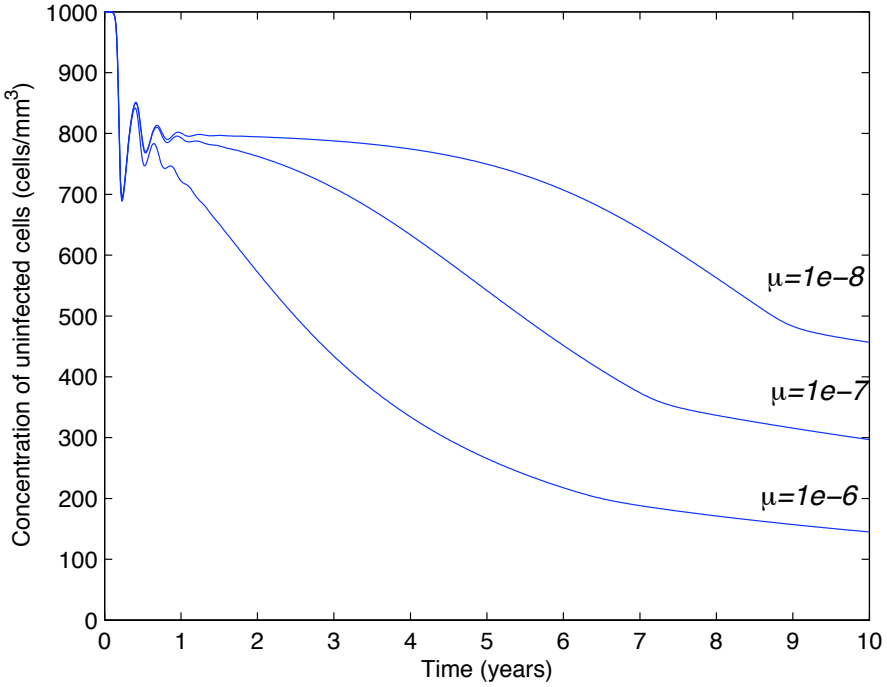
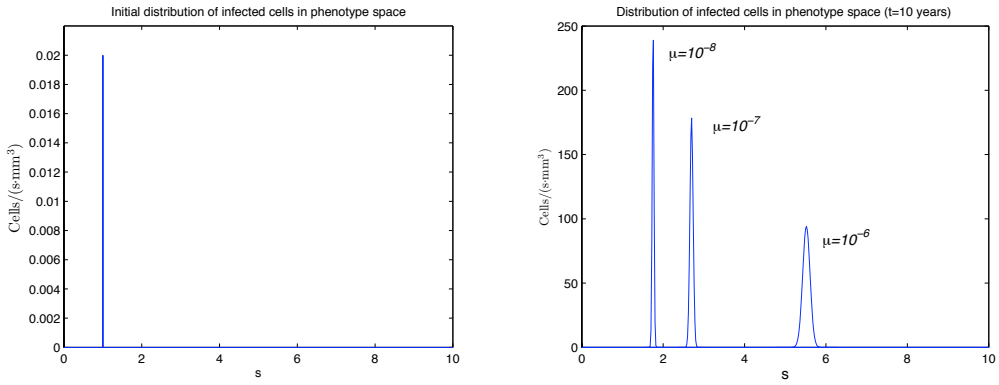


FIGURE 2. The dynamics of the uninfected $CD4^+$ T cells levels for 10 years for $\mu = 10^{-6}$, 10^{-7} and 10^{-8}.

where viral strain are assumed to be continuously distributed in a 1-dimensional phenotype space and a possibility of random mutation of the virus is incorporated. Numerical simulations with this model demonstrated that random mutations combined with competition for a resource (the target cells in this case) result in evolution towards higher Darwinian fitness.

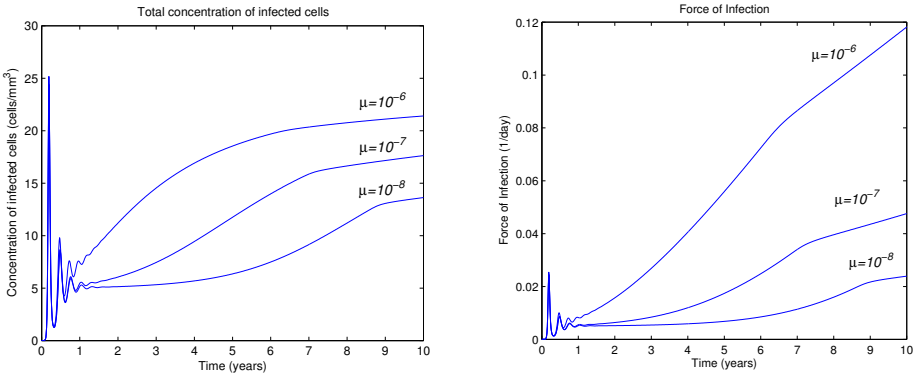
Numerical simulations show that the speed of evolution is not constant but depends on the infectivity of strains and the abundance of target cells. For relatively low values of the diffusion coefficient, this dependence leads to the dynamics which is qualitatively very similar to the typical dynamics of HIV infection: following the transition period, there is a prolonged period of relatively slow evolution (and a slow decreasing of the $CD4^+$ T cells level), which follows by a period of a fast acceleration of evolution (and hence by an abrupt drop of the $CD4^+$ T cells level). This dynamics is very similar to the asymptomatic stage of HIV infection, which ends with a rapid drop of the $CD4^+$ T cells level and a development of AIDS.

Immune response is not included in the model, and the results demonstrate that this is not necessary for evolution. This, however, does not mean that the immune response have no impact on evolution at all. On contrary, based on the



(A) (B)

FIGURE 3. Distribution of infected cells in the strain space; here (a) is the initial distribution, and (b) are distributions after 10 years for $\mu = 10^{-8}$, 10^{-7} and 10^{-6}. Please note different vertical scales in (a) and (b).



(A) (B)

FIGURE 4. The dynamics of infected population (a) and the infective force (b) for 10 years for $\mu = 10^{-8}$, 10^{-7} and 10^{-6}.

analysis of the results, one can come to a conclusion that, if immune response does not eliminate virus, then it increases the speed of evolution. Simulations show that the speed of evolution directly depends on the abundance of the target cells, and therefore a possible mechanism of this increase of speed of evolution due to immune response is not a positive selection (even if this can make an effect as well) but rather reducing competing pressure on newly emerging strains and thus, by eliminating earlier emerged less fit strains, providing more target cells for more fit strains.

Acknowledgments

A.K. is supported by the Ministry of Science and Innovation of Spain via Ramón y Cajal Fellowship RYC-2011-08061.

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