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Synaptic transmission may provide an evolutionary benefit to HIV through modulation of latency

Cesar Vargas-Garcia[a,*], Ryan Zurakowski[a], Abhyudai Singh[b]

[a] Fundación Universitaria Konrad Lorenz, Bogotá, Colombia
[b] Department of Electrical and Computer Engineering, Biomedical Engineering, Mathematical Sciences, University of Delaware, Newark DE 19716, USA

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ABSTRACT

Transmission of HIV is known to occur by two mechanisms in vivo: the free virus pathway, where viral particles bud off an infected cell before attaching to an uninfected cell, and the cell-cell pathway, where infected cells form virological synapses through close contact with an uninfected cell. It has also been shown that HIV replication includes a positive feedback loop controlled by the viral protein Tat, which may act as a stochastic switch in determining whether an infected cell enters latency. In this paper, we introduce a simple mathematical model of HIV replication containing both the free virus and cell-cell pathways. Using this model, we demonstrate that the high multiplicity of infection in cell-cell transmission results in a suppression of latent infection, and that this modulation of latency through balancing the two transmission mechanisms can provide an evolutionary benefit to the virus. This benefit increases with decreasing overall viral fitness, which may provide a within-host evolutionary pressure toward more cell-cell transmission in late-stage HIV infection.

1. Introduction

The Human Immunodeficiency Virus (HIV) is a retrovirus that primarily targets the CD4+ T-cells. While it is susceptible to antiviral compounds at several points during its life cycle, it is capable of creating replication-competent chromosome-integrated infections with very little viral transcription (Finzi et al., 1999; 1997). These so-called quiescently-infected cells are not affected by any of the current antiviral compounds (Dinoso et al., 2009). Such quiescent or latent cells can persist for decades before randomly transitioning to a fully activated, virus producing state, and constitutes a major barrier to eradicating the virus from a patient (Richman, 2011; Richman et al., 2009; Siliciano and Siliciano, 2013).

The HIV cell-fate decision of whether to follow a latent or active-infection pathway is critically controlled through a positive-feedback loop mediated by the Tat viral protein (Karn and Stoltzfus, 2012; Razooky et al., 2015; Singh, 2012; Singh and Weinberger, 2009; Weinberger et al., 2005). Tat facilitates the successful transcription of the integrated HIV genome (Laspia et al., 1989). When Tat is suppressed, little to no viral transcription is observed Mousseau et al. (2015). Conversely, when exogenous Tat is supplied, latency is suppressed (Donahue et al., 2012). Once successful transcription has occurred, translation provides an adequate number of Tat molecules to facilitate continued transcription and translation, providing the positive feedback mechanism.

As HIV transcription, translation, and assembly progress in an infected cell, the HIV surface molecules gp120 and gp41 begin to accumulate on the surface of the infected cell (Roy et al., 2013). These molecules have a high affinity for the CD4 and CCR5 molecules on T Cells, and facilitate the binding and membrane fusion processes during infection by free virions. However, the molecules on the surface of the infected cell can also facilitate the formation of synapses between infected cells and uninfected T Cells (Muranyi et al., 2013). This is recognized as a major secondary pathway for HIV transmission, in addition to the free virus pathway (Sigal et al., 2011).

The synaptic pathway results in the equivalent of a large number of virions being deposited into the target cell; this is referred to as multiplicity of infection. While this increases the probability of a successful infection, it does so at the cost of forgoing the possibility of infecting other target cells via the free virus pathway. Potential evolutionary advantages and disadvantages of utilizing the synaptic pathway of transmission have been previously examined in several works (Komarova et al., 2013a; 2012; 2013b; Komarova and Wodarz, 2013; Sigal et al., 2011; Vargas Garcia et al., 2013). We propose a novel explanation for the evolution of the synaptic pathway; the modulation of the probability of latency.

* Corresponding author.
E-mail addresses: cavargar@udel.edu, cesara.vargasg@konradlorenz.edu (C. Vargas-Garcia), ryanz@udel.edu (R. Zurakowski), absingh@udel.edu (A. Singh).

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Modulation of latency through the balance of synaptic and free virus transmissions pathways occurs in the following way. An initial, randomly distributed number of Tat molecules are transmitted during infection. These molecules may reside in the virion (Chertova et al., 2006), or they may be secreted by the parent cell and subsequently endogenized by the target cell (Debaisieux et al., 2012). The more Tat molecules are present, the more likely that transcription will complete before the initial Tat molecule population degrades. Cells infected via the synaptic pathway have many times more Tat molecules present at infection than cells infected via the free virus pathway. This dramatically reduces the probability that cells infected by the synaptic pathway will enter a latent state.

In this paper, we introduce a simple mathematical model of HIV replication that accounts for both the free virus and cell-cell transmission pathways. The dynamics include the effect described above, namely that the likelihood of an infected cell entering a latent state is reduced if that cell was infected via the cell-cell pathway as compared to a cell infected by the free virus pathway. We demonstrate through mathematical modeling that viruses with the cell-cell transmission pathway have a selective advantage compared to viruses without this mechanism, with an optimal fraction of total virus transmitted through the synaptic pathway ranging between 0% and 20%, depending primarily on the per virus probability of infection, the probability that a cell infected by a single virus will enter latency, and the basic reproductive ratio of the free-virus pathway. We also show that the optimal fraction of viruses sent through the synaptic pathway dramatically increases as the basic reproductive ratio of the free virus pathway decreases. We hypothesize that this may create a pressure for within-host evolution toward virus that promotes cell-cell binding, which may lead to syncytia formation in late-stage HIV disease.

2. HIV model

The free virus transmission mechanism is described using the extensively studied model introduced in Perelson (1993). In this model the behavior of uninfected, infected cells and HIV virus is given by

$$\dot{T} = \underbrace{\lambda}_{\substack{\text{T}-\text{cell}\\ \text{Production}}} - \underbrace{d_T T}_{\substack{\text{T}-\text{cell}\\ \text{Death}}} - \underbrace{\beta_f T V_f}_{\substack{\text{Free Virus}\\ \text{Infection}}} \tag{1a}$$

$$\dot{I}_f = \underbrace{\beta_f T V_f}_{\substack{\text{Free Virus}\\ \text{Infection}}} - \underbrace{d_I I_f}_{\substack{\text{Infected Cell}\\ \text{Death}}} \tag{1b}$$

$$\dot{V}_f = \underbrace{k I_f}_{\substack{\text{Free Virus}\\ \text{Production}}} - \underbrace{d_V V_f}_{\substack{\text{Free Virus}\\ \text{Death}}}. \tag{1c}$$

Here $T(t)$, $I_f(t)$ and $V_f(t)$ represent uninfected cells, infected cells and free virus populations. The rate of production of uninfected cells is represented by λ. Death rates of uninfected cells, infected cells and free virus are d_T, d_I and d_V respectively. k represents the number of free virus particles produced per infected cell per time unit. The mass-action infection rate is given by β_f. Table 1 shows these parameters and nominal experimentally-fitted values for them obtained in Luo et al. (2012).

If we assume that half-life of free virus is much smaller than that of infected cells ($d_V >> d_I$), then the virus population can be assumed to be approximately in quasi-steady state, and $V_f \approx \frac{k}{d_V} I_f$. Thus Eq. (1) reduces to

$$\dot{T} = \lambda - d_T T - \frac{k}{d_V} \beta_f T I_f \tag{2a}$$

$$\dot{I}_f = \frac{k}{d_V} \beta_f T I_f - d_I I_f. \tag{2b}$$

The basic reproductive ratio of infection by the free virus pathway is given by:

$$R_{0f} = \frac{\lambda k \beta_f}{d_V d_I d_T}. \tag{3}$$

If $R_0 > 1$ then the disease free condition of Eq. (2) is unstable and the infection will converge to an infected steady-state.

3. Modeling synaptic virus

Eq. (1) describes transmission by free pathway. However that is not the only method of HIV transmission. Infection may also occur through direct interaction between cells, a process called synaptic transmission. When T cells come into close contact with other T cells, they sometimes form structures known as viral synapses (Jolly et al., 2004). When infected and uninfected cells form synapses, this facilitates the transfer of a large number of virions from the former to the latter (Hübner et al., 2009; Jolly et al., 2004). This cell-to-cell transmission of HIV requires the assembly of enveloped virus particles. The increased efficiency of this infection route observed in experiments likely results from the high local concentrations of virus particles at sites of cellular contacts rather than from a qualitatively different transmission process. Since there is no difference in the assembly processes, intracellular processes in both target and infected cells might be similar in both transmission modes (free and synaptic pathway).

In *in-vitro* cell cultures, viruses may display two types of replication strategies: cell-free and cell-to-cell infection by means of synapse formation. In our model, we refer to V_s as a viral strain displaying both replication types. We modify Eq. (1) in order to model synaptic transmission. Let $V_s(t)$ and $I_s(t)$ be population of free virus originating from a cell population capable of forming synapses and infected cells capable of forming a synapse at time t, respectively. Also let s be the synaptic size, which is the number of virions transmitted through a single synapse. Infected cells can now be formed through free virus infection at a rate $\beta_f T V_s$, as well as through synapse formation at a rate $p(s)\beta_s T I_s$. Here β_s is the rate of interaction between infected and uninfected cells. The function $p(s)$ is the probability that an uninfected cell will become infected after receiving s virus particles through a synapse. The probability $p(s)$ is defined as

$$p(s) = \sigma f(s), \tag{4}$$

where σ is the probability that uninfected and infected cell form synapses given there is interaction, $f(s)$ is the probability that sending s viruses through given synapses leads to an infection, and can be any monotonically increasing function on s. If we assume that each of s copies has an independent chance of successfully infecting the host cell, with each virus copy having probability r of successful infection then $f(s)$ has the form:

$$f(s) = \left(1 - (1-r)^s\right), \tag{5}$$

i.e. $f(s)$ is the probability that at least one of s virus has successful infection given there is synapses.

There are two possible scenarios for synapse formation: infected cells with uninfected cells and infected cells with infected cells. The former leads to an infection with probability $p(s)$. Therefore there is a reduction of $s\sigma\beta_s T I_s$ virus copies that cannot be used in further infections. The other scenario arises because there

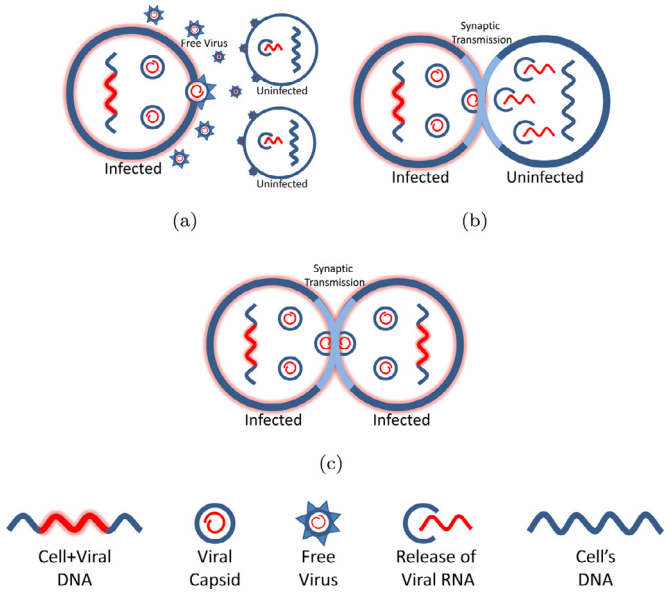

Fig. 1. Synaptic virus mechanism. A synaptic virus has the capability of infecting cells by means of free pathway (a) and also through synapses formation (b). In the free pathway (a), infected cells produce RNAs (red lines) using virus information stored in its genome (blue and red line), encapsules them (blue and red concentric circles) and send this capsids outside the cell. Uninfected cells absorb them releasing virus RNAs (opened blue circle) which integrates with cell's DNA (blue line). Synaptic interactions may occur between infected and uninfected (b) or infected-infected cells (c). The virus copies in (b) sent through synapses are not used in the infection of other cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is no known discrimination mechanism that leads infected cells to form synapses with uninfected cells only, thus infected-infected interactions also should occur. Infected-infected synapses lead to a waste of $s\sigma\beta_s I_s^2$ virus copies that does not produce any additional infection, because both cells are already infected. Fig. 1 shows all three possible infection pathways: free virus transmission, infected-uninfected and infected-infected virus transmission through synapses.

Using the synaptic mechanism illustrated above and including it in (1) leads to

$$\dot{T} = \lambda - d_T T - \beta_f T V_s - \underbrace{p(s)\beta_s T I_s}_{\text{Synaptic Infection}} \tag{6a}$$

$$\dot{I}_s = \beta_f T V_s - d_I I_s + \underbrace{p(s)\beta_s T I_s}_{\text{Synaptic Infection}} \tag{6b}$$

$$\dot{V}_s = k I_s - \underbrace{s\sigma\beta_s (T + I_s) I_s}_{\text{Reduction of Virus Production}} - d_V V_s. \tag{6c}$$

Note that k and s are the amount of virus inside the cell before being released and the amount of virus send through synapse, respectively. The consumption term $s\sigma\beta_s (T + I_s) I_s$ corresponds to the amount of virus to be delivered by cell-to-cell interaction at a given moment.

Again, if we take advantage of the fact that free virus copies die at a much greater rate than infected cells ($d_V >> d_I$), then the virus is almost always in quasi-steady state ($V_s = \left(1 - \frac{s}{k}\sigma\beta_s (T + I_s)\right)\frac{k}{d_V} I_s$) and Eq. (6) reduces to

$$\dot{T} = \lambda - d_T T - \left(1 - \frac{s}{k}\sigma\beta_s (T + I_s)\right)\frac{k}{d_V}\beta_f T I_s - p(s)\beta_s T I_s \tag{7a}$$

$$\dot{I}_s = \left(1 - \frac{s}{k}\sigma\beta_s (T + I_s)\right)\frac{k}{d_V}\beta_f T I_s - d_I I_s + p(s)\beta_s T I_s, \tag{7b}$$

which have two stationary points, one of them being the uninfected state

$$T = \frac{\lambda}{d_T},\ I_s = 0. \tag{8}$$

Infection will occur (this point is unstable) if

$$R_{0s} = \left(1 - \frac{s}{k}\sigma\beta_s\frac{\lambda}{d_T}\right)R_{0f} + p(s)\beta_s\frac{\lambda}{d_I d_T} > 1. \tag{9}$$

The other stability point is not difficult to calculate, however is not included here due to space limits.

4. Modeling effects of synaptic transmission mechanisms on HIV latency reservoirs

Single infection produced by the free pathway leads to two distinct situations for the new infected cell: transforms it into an active cell or latent infected cell. In the active state, the infected cell produces new viruses until it dies (lysis). When it goes latent, this infected cell does not produce new viruses. Adding the synaptic transmission mechanism can dramatically reduce the production of latent cells. This is because it allows multiple infections in a single cell, which proportionally increases the bolus of the HIV molecule Tat which is transmitted. According to the hypothesis that the cell-fate decision of a newly infected cell to become active or latent is largely due to the stochastic presence or absence of sufficient Tat to promote the early transcription of HIV, this should decrease the probability of a cell infected by the synaptic pathway of becoming latent. Fig. 2 describes the possible outcomes of infection for both the free virus and synaptic transmission mechanisms.

In order to study how the synaptic mechanism affects HIV persistence, we add a latently infected cells pool L_s. Synaptic infection effect splits now into two pools: the active, with probability

$$\alpha(s) = \sum_{i=1}^{s}\binom{s}{i} r^i (1-r)^{s-i}\left(1 - \rho^i\right), \tag{10}$$

and the latent, with probability

$$\eta(s) = \sum_{i=1}^{s}\binom{s}{i} r^i (1-r)^{s-i}\rho^i. \tag{11}$$

$\alpha(s)$ and $\eta(s)$ are the probability of s or fewer virus particles sent through synapses produce an active and a latent infected cell, respectively. ρ is the probability that a cell infected with a single viral copy will become latent. The probabilities take this form based on the assumption that all of the independent infection events occurring with probability r would have a probability ρ of producing a latent infection if the infection is successful, but if any of them do not produce a latent infection, the outcome is an actively infected cell. Note that $\alpha(s) + \eta(s) = f(s)$. The latently infected cells are also targets for formation of dead-end synapses that waste virus as mentioned before; it is assumed that infection of these cells does not affect their state of latency. Including all these new

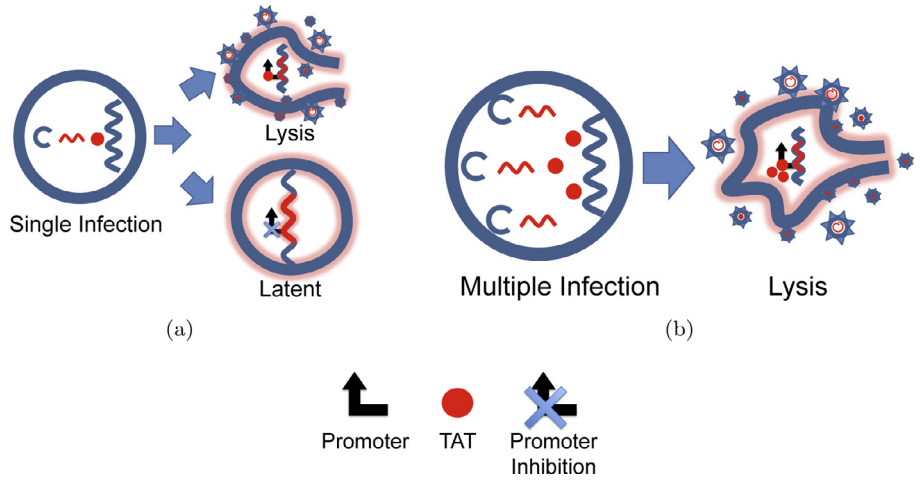

Fig. 2. Effects of free and synaptic mechanisms on the latent pool. Free virus transmission mechanism results in a single infection with low Tat copy number, compared with synaptic transmission, that may lead the production of new viruses and subsequent lysis of the infected cell or the formation of a latent infection (a). Synaptic transmission results in a multiple infection with high Tat copy number that reduces the probability of producing latent infection (b).

assumptions into Eq. (6) leads to the system

$$\dot{T} = \underbrace{\lambda}_{\substack{\text{T-cell}\\ \text{Production}}} - \underbrace{d_T T}_{\substack{\text{T-cell}\\ \text{Death}}} - \underbrace{\beta_f T V_s}_{\substack{\text{Free}\\ \text{Mechanism}}} - \underbrace{p(s)\beta_s T I_s}_{\substack{\text{Synaptic}\\ \text{Mechanism}}} \tag{12a}$$

$$\dot{I}_s = \underbrace{(1-\rho)\beta_f T V_s}_{\substack{\text{Free Active}\\ \text{Infection}}} - \underbrace{d_I I_s}_{\substack{\text{Infected}\\ \text{Death}}} + \underbrace{\alpha(s)\beta_s T I_s}_{\substack{\text{Synaptic}\\ \text{Active}\\ \text{Infection}}} + \underbrace{a_L L_s}_{\substack{\text{Latent}\\ \text{Activation}}} \tag{12b}$$

$$\dot{L}_s = \underbrace{\rho\beta_f T V_s}_{\substack{\text{Free Latent}\\ \text{Infection}}} - \underbrace{d_L L_s}_{\substack{\text{Latent}\\ \text{Death}}} - \underbrace{a_L L_s}_{\substack{\text{Latent}\\ \text{Activation}}} + \underbrace{\eta(s)\beta_s T I_s}_{\substack{\text{Synaptic Latent}\\ \text{Infection}}} \tag{12c}$$

$$\dot{V}_s = \underbrace{k I_s}_{\substack{\text{Free Virus}\\ \text{Production}}} \underbrace{- s\sigma\beta_s (T + I_s + L_s) I_s}_{\substack{\text{Reduction}\\ \text{of Virus}\\ \text{Production}}} - \underbrace{d_V V_s}_{\text{Virus Death}}. \tag{12d}$$

For the remainder of the paper we use the values $0 < \rho < 0.9$ as the probability that a new infection becomes latently infected. These values include cases in which there is not latent pool ($\rho = 0$) and where most of the infections become latent ($\rho \approx 0.9$). The probability that there is cell-to-cell (synapse formation) upon cell encounter is assumed to be $\sigma = 1$. We expect the probability of infection by one virus copy sent through synapse to take a small value ($r < 0.1$) given the large number of copies sent. We assume reactivation and death rate of latently infected cells to be 10 times slower than the death rate of a normal cell ($a_L < 0.01$, $d_L < 0.01$).

5. Evaluating fitness

The above equations describing the regulation of latency via synaptic virus transmission are analyzed to determine the conditions where synaptic transmission gives a fitness benefit to the virus. The standard measure for fitness, the basic reproduction ratio R_0, is not appropriate in this circumstance, as the mechanism by which latent virus gains an advantage depends on the behavior as target cells become scarce, and R_0 considers only the condition when target cells are at maximum abundance. As shown in Fig. 3,

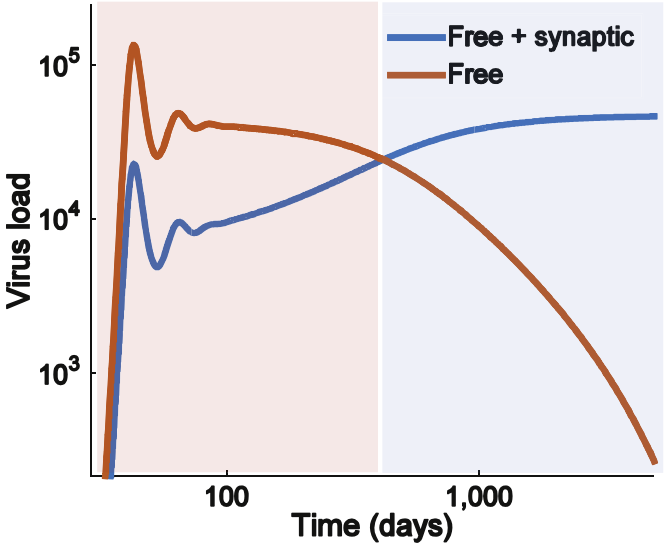

Fig. 3. Although $R_{0f} > R_{0s}$ ($2 > 1.88$), the synaptic virus invades the free virus. Here R_{0f} and R_{0s} were computed numerically using Equation 12 (Please see S1 for details). Parameters used were $s = 1870$, $\rho = 0.01$, $a_L = 0.003$, $r = 0.05$, $\sigma = 1$ and the parameters from Table 1. In this case, viral fitness is determined by steady-state virus load instead of R_0.

Table 1
Data shown in this table (except β_s) are close to the values obtained from posterior distribution of parameters for a commonly used HIV infection model identified against measured patient data (Luo et al., 2012). β_s was estimated by assuming the steady-state rate of infections by the free virus pathway is 20 times greater than rate of infections by the synaptic pathway.

Parameter	Value	Units	Biological meaning
λ	7×10^2	$\frac{cells}{\mu L \times day}$	Uninfected birth rate
d_T	0.1	$\frac{1}{day}$	Uninfected death rate
d_I	1	$\frac{1}{day}$	Infected cells death rate
d_V	23	$\frac{1}{day}$	Virus death rate
k	2×10^3	$\frac{copies}{cell \times day}$	Copies of virus per cell
β_f	2×10^{-6}	$\frac{mL}{copies \times day}$	Rate of uninfected-virus interaction
β_s	10^{-5}	$\frac{\mu L}{cell \times day}$	Rate of infected-uninfected interaction

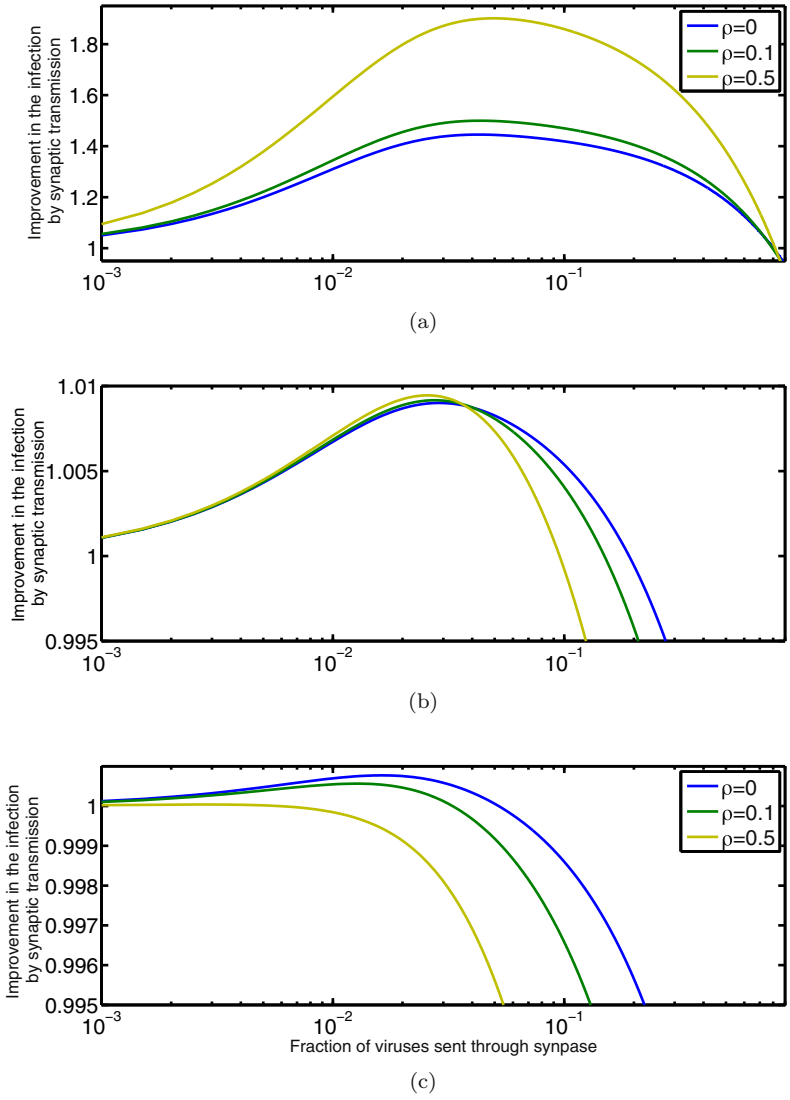

Fig. 4. The ratio of infected cell count at equilibrium for a virus capable of synaptic transmission to a virus incapable of synaptic transmission as a function of the fraction of total virus production committed to synaptic transmission, where the basic reproductive ratio of the synaptic transmission-free virus is (a) 1.2, (b) 4, (c) 10. The value of r is 0.05 in all cases. Reactivation and death of latently infected cells are $a_L = 0.01$ and $d_L = 0.01$, respectively. The fraction of viruses sent through synapse is defined by s/k where $k = 2 \times 10^3$.

it is quite easy to show that for many values of the parameters the virus with the synaptic mechanism has a lower R_0, and yet outcompetes the virus without the synaptic transmission mechanism, and eventually drives it extinct.

For these reasons, instead of R_0, we use the steady-state infected cell count as our measure of fitness. Using this fitness criterion, the ability of the virus to devote some of its virus production to the synaptic transmission pathway shows a clear evolutionary benefit, which is stronger when the R_0 of the free virus pathway is smaller. Fig. 4 shows the ratio of steady-state virus loads for free virus R_0 values of 1.2, 4, and 10 plotted against the fraction of virus produced which are used in synaptic transmissions.

The fitness benefit reaches a maximum for moderate levels of synaptic transmission, representing between 1% and 10% of the total virus produced; the exact maximum synaptic fraction and the actual benefit obtained depends primarily on the free virus R_0 and the probability ρ that a cell infected by a single virus enters latency. The greatest benefit is seen for small free virus R_0 and high ρ, whereas for large free virus R_0 and high ρ no benefit is obtained via the synaptic virus mechanism. The dependence on ρ illustrates the benefit obtained by synaptic transmission through its ability to modulate the percentage of infected cells entering latency, and reducing this fraction when target cells are abundant.

To evaluate the evolutionary benefit of synaptic transmission, we studied the hypothetical situation in which both free-only pathway and synaptic-capable viruses are competing for the same target population. Therefore, when a composite model containing both species is considered, we found that the zero synaptic virus steady state is unstable, thus any small initial population of synaptic virus will become established.

Additionally, we studied the invasion criterion of the synaptic virus: the parameter values for which synaptic transmission provides an evolutionary benefit and would therefore invade a population of virus incapable of forming synapses. Analysis shows that the invasion criterion is independent of the per virion infection probability r, but depends on the probability of latency for a single virus infection ρ, the fraction of viruses sent via the synaptic pathway, and the infectivity ratio of the free virus pathway R_0. These threshold values are illustrated in Fig. 5 (a). For any values of the fraction of virus sent through the synaptic pathway below these critical values, the synaptic pathway provides an evolutionary benefit over the free virus pathway alone. This shows that an

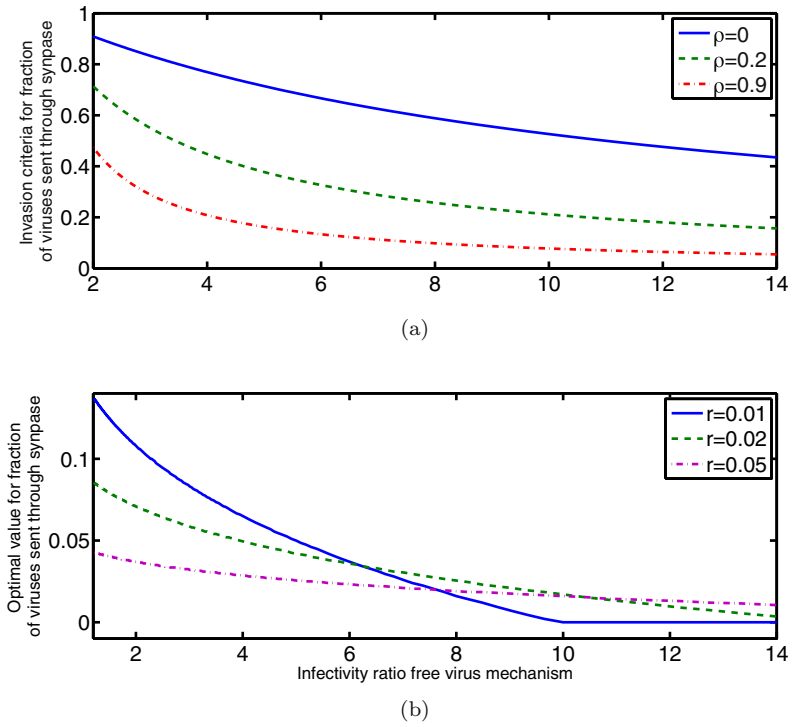

Fig. 5. The invasion criterion (a) and optimal value (b) for the fraction of total virus production committed to synaptic transmission is plotted versus the infectivity ratio of the free virus mechanism. The invasion criterion is independent of r, and is plotted for different values of p. For panel (b), p=0.01. Reactivation and death of latently infected cells are $a_L = 0.01$ and $d_L = 0.01$, respectively.

evolutionary benefit persists even when a remarkably high fraction of the virus production is dedicated to the synaptic transmissions. The optimal value for the fraction of virus dedicated to synaptic transmission is much lower, however, and depends greatly on r; this is shown in Fig. 5 (b) for several values of r and a fixed value of $\rho = 0.01$.

6. Discussion

We have introduced a novel mathematical model of synaptic virus transmission and analyzed its behavior across a range of possible parameter values. This model shows that synaptic transmission provides an evolutionary benefit despite decreasing the basic reproductive ratio. This benefit increases with decreasing free virus reproductive ratio R_0 and has a complex relationship with the probability of latency ρ and the per virion infection rate r, with the sensitivity of the evolutionary benefit to these parameters changing sign as R_0 increases. Of particular interest is the consistent trend shown in Fig. 5 where decreasing R_0 results in increases both in the optimal fraction of virus committed to the synaptic pathway and the evolutionary benefit of the synaptic pathway. This may explain an observed feature of within-host evolution of HIV. During early HIV infection, the measured R_0 of the virus is very high, with estimates ranging between 8 and 20 (Ribeiro et al., 2010), which reduces to between 2 and 3 during chronic infection (Luo et al., 2012). Furthermore, viral phenotype during transmission and early infection is nearly always dominated by a CCR5-tropic phenotype (Michael et al., 1997), but untreated infections follow a predictable pattern of within-host evolution, with the virus becoming dominated by strains that use the CXCR4 co-receptor (Scarlatti et al., 1997). CXCR4-tropic virus strains are associated with increased formation of tight junctions and syncytia (Troyer et al., 2005), which facilitate cell-cell transmission (Sloan et al., 2013);they are also associated with more rapid declines in CD4+ T-Cell counts and overall disease progression (Connor et al., 1997). While both CCR5-tropic and CXCR4-tropic virus can both facilitate cell-cell transmission to a degree, we hypothesize that the strong preference for CCR5-tropic during transmission and acute infection may be at least partially attributed to the evolutionary disadvantage associated with the cell-cell pathway when the free-virus R_0 is high, and that the subsequent pattern of evolution of co-receptor diversity may be attributed to the shift toward a strong evolutionary benefit for the cell-cell pathway once the free virus R_0 decreases during chronic infection.

Our model assumes that on infection, an activated CD4+ T-Cell has a probability of becoming actively or latently infected. However, it is not clear how active and latent infection is established. In vitro evidence has suggested that HIV predominantly replicates in activated rather than resting CD4+ T-Cells. Moreover, in vivo, most HIV-infected resting CD4+ T-Cells exhibit a memory phenotype, suggesting that they arose from the infection of previously activated CD4+ T-Cells. This observation supports the theory that latency is established from infected activated CD4+ T-Cells that fall into a resting memory state. However, these actively infected cells need to survive cytophatic effects and fast immune response which are the main reasons for their short half life. To bypass this adverse situations and produce latent infection, the virus might infect just at the moment when active CD4+ T-Cells are transitioning to the resting mode (Chavez et al., 2015). Recent studies have shown that direct infection of resting CD4+T is also possible and leads to both latent and active infected cells. All this alternative sources of active and latent infection can be incorporated in our model in a straightforward way if we assume that the population of target cells T include both active and resting CD4+ T-Cells. The probability of becoming latent ρ is then the probability of a virus infecting either an active CD4+T cell which further will revert to resting state or an already resting CD4+T cell. This new definition of ρ will lead to similar conclusions when analyzing our model.

Whether coinfection of latently infected cell via free virus pathway is possible remains elusive. Brégnard et al. (2012) showed that

the number of cells expressing a virus reporter after incubation with HIV increased when these cells were exposed to Tat. This observation suggested that co-infection with HIV activated latently infected cells. Despite this, there is only a small fraction of cells that are ever infected by the virus, thus a vanishingly small fraction will be infected twice or co-infected. Although initially our model excludes super-infection to any extent, we could add this in a straightforward manner by transforming a fraction of every encounter between virus an latently infected cells into an active infection. We expect that doing so, the synaptic virus might have more options when selecting the amount of viral copies to sent through the synapse and therefore invade the free virus strain. Thus we will see and increase in the limiting value shown in Fig. 5 a. This increase in the limiting value could be explained by the fact that superinfection increases the number of active infections that will take advantage of the synaptic pathway.

It is unclear whether transfer of HIV-1 through cell-to-cell contact triggers the same innate immune responses as free virus pathway in resting CD4 T cells, the predominant target cells depleted by HIV in lymphoid tissues. Recent studies have shown that synaptic transmission is the main reason of CD4-T cell depletion (Galloway et al., 2015). This implies that despite the high infectivity rate of the synaptic pathway, only a portion of cell-to-cell contacts between infected and uninfected cells become new infections. The remaining result into pyroptosis death of resting CD4-T cells. It remains to be determined if these deaths reduces the infectivity rate of synpase pathway, from $10^2 - 10^3$ times free pathway infectivity to only a fraction of it. It is also not clear whether the high rate of pyroptosis observed in vitro also occurs in vivo. One way of extending our model to include this complex phenomena is by killing latently infected cells upon successful infection via synaptic pathway. Simulations of this modified model suggest a decrease in the critical value of viral copies sent through synapse that produce and evolutionary advantage, especially in situations where the infectivity ratio is large. This is expected given the fact that superinfection reduce the latent pool that potentially will produce active infections.

A recent study found that virus dynamics models that exclude pyroptosis, superinfection, or other potential complexities are unable to reproduce data on latent infection pools (Wodarz and Levy, 2017). Those complexities might be produced by intricate cell-to-cell interactions like synapse formation. As per Wodarz and Levy (2017), our model shows that cell-to-cell interactions might drive the size of the latent pool. Our model, however, suggests that the increase in the likelihood of a new infection becoming active instead of latent might explain reduced size in the latent pool seen in experiments and clinical data as well. Taking into account both models, synaptic transmission shapes latent pool by both increasing the likelihood of pyroptosis or superinfection and reducing the likelihood of new infections becoming latent.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtbi.2018.07.030.

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