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A stochastic spatio-temporal (SST) model to study cell-to-cell variability in HIV-1 infection

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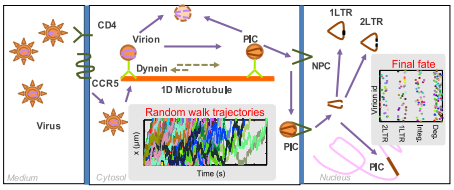
HIGHLIGHTS

- We developed a stochastic intracellular mathematical model of HIV replication.
- The model includes spatial microtubule transport of viral components.
- The model can simulate single round infections and viral fates.
- The model predicts that vRNA decay and RT are critical determinants of integration.

GRAPHICAL ABSTRACT



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ABSTRACT

Although HIV viremia in infected patients proceeds in a manner that may be accounted for by deterministic mathematical models, single virus-cell encounters following initial HIV exposure result in a variety of outcomes, only one of which results in a productive infection. The development of single molecule tracking techniques in living cells allows studies of intracellular transport of HIV, but it remains less clear what its impact may be on viral integration efficiency. Here, we present a stochastic intracellular mathematical model of HIV replication that incorporates microtubule transport of viral components. Using this model, we could study single round infections and observe how viruses entering cells reach one of three potential fates – degradation of the viral RNA genome, formation of LTR circles, or successful integration and establishment of a provirus. Our model predicts global trafficking properties, such as the probability and the mean time for a HIV viral particle to reach the nuclear pore. Interestingly, our model predicts that trafficking determines neither the probability or time of provirus establishment – instead, they are a function of vRNA degradation and reverse transcription reactions. Thus, our spatio-temporal model provides novel insights into the HIV infection process and may constitute a useful tool for the identification of promising drug targets.

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1. Introduction

Human immunodeficiency virus (HIV) is an enveloped single-stranded RNA virus. The most common and natural route of HIV infection is via sexual mucosal transmission. There are different time scales associated with the infection process. At the early stages (usually in the first few hours post infection), HIV will cross the mucosal barrier and only a small number of cells are successfully infected; these constitute the seed or founder population, which after several days start production of new virus. Within the first week, lymphatic tissue reservoirs will trigger the conversion to the seropositive infection state. Thus, the early phases of HIV exposure and infection are of critical importance, and they are believed to provide a window of opportunity that determines sero-conversion, as well as – if sero-conversion cannot be prevented – the viral set point that determines collapse and

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amplification processes (Haase, 2010). Thus early phase infection events are critical in determining the fate of the exposed individual. Here, we present a mathematical framework to address the stochastic nature of the early phases of the HIV life cycle, namely from docking to establishment of a provirus.

The HIV life cycle begins when the envelope (Env) glycoprotein (gp120) binds to the host surface receptor (CD4) and co-receptor (CCR5 or CXCR4). Then the virion either fuses with host cell membranes in a pH-independent manner (Stein et al., 1987) or via an alternative endocytic pathway (Miyauchi et al., 2009). Once inside the cell, the virus is transported across the actin layer and undergoes uncoating to generate the viral reverse transcription complex (RTC), which comprises the diploid viral RNA genome, tRNALys primer, RT, IN, MA, nucleocapsid (NC), viral protein R (Vpr) and various host proteins. Once the RTC reaches close to nuclear pore complex (NPC) via microtubule, they will dock to NPC and undergoes DNA-Flag-dependent maturation, forming a pre-integration complex (PIC) (Arhel et al., 2007). Then the PIC translocate through the nuclear pore to get inside of the nucleus. In the nucleus, the PIC can either integrate into the host chromatin or circularizes into 1- or 2 LTR circles.

A large portion of the early HIV life cycle is taken up by transcellular transport that moves the virus from the plasma membrane to the nuclear pore (Brandenburg and Zhuang, 2007). It is found that after fusion, the virus will go through three kinetically distinguishable directed movements until it reaches the nuclear surface. It first travels across one actin layer with a random diffusion, then binds to the microtubule and trafficks along it until reaching the proximal of the nuclei, where it has to cross another actin layer to reach the NPC on the nuclear membrane (Arhel et al., 2006; McDonald et al., 2002). How trafficking relates to infectivity is an important question.

Mathematical modeling has been applied at different levels of HIV infection rendering quantitative insights. Perhaps, the most established models are those of viral dynamics within patients (Perelson, 2002).They focus on the dynamics of virion numbers and numbers of different cell types during the HIV infection and AIDS development. At the molecular level, molecular dynamic simulations were used to study kinetic mechanisms of the HIV-1 viral protein conformational transitions (Deng et al., 2011). At the intracellular level, a detailed deterministic model was proposed by John Yin's group (Reddy and Yin, 1999), with other simplified models for different focus. Weinberger developed a small stochastic model to study the HIV gene expression and replication (Weinberger et al., 2005). Kim and Yin proposed a model to study different splicing products during HIV replication (Kim and Yin, 2005). Later, Althaus and De Boer presented a combination of the models developed by Weinberger and Reddy to study the relationship between viral transcription and the viral load during drug therapy (Althaus and De Boer, 2010). These models account for mechanistic details about HIV intracellular replication, though they exclude intracellular transport of viral components. Dinh developed such models to study adenoviral vectors transportation (Dinh et al., 2005; Dinh et al., 2007) in the context of gene therapy, but how trafficking and biochemical reactions combine to give rise to HIV replication remains elusive. Here we present a model that couples reactions with transport and provides a more accurate description of HIV replication in agreement with recent experimental observations.

An infection may be initiated by a single virus particle that delivers its genome, a single molecule of RNA, to its host cell. Under such conditions, the inherent fluctuations in the levels of viral constituents may yield qualitatively different behavior (Srivastava et al., 2002). Deterministic models that describe the expected progress of the infection cannot be employed to predict the probability of infection establishment at the primary stage (Khalili and Armaou, 2008). In this study, we integrate the HIV transport with basic HIV life cycle model and establish a stochastic spatio-temporal model to study early HIV infection. The model can track each infected single virus's life cycle. Three different fates of the virus can be recapitulated by the model. We also used the model to study the effects of each parameter on the integration fraction and time to integration.

2. Methods

We first developed an ODE model to derive kinetic parameters for key reactions in the HIV life cycle from recent experimental results of a fine-grained timecourse (Mohammadi et al., 2013). We then developed the SST model (Fig. 1A) using those parameters. The overall model development process is shown in Fig. 1B.

2.1. An ODE model to derive parameters

As the *in vitro* infection experiment (Mohammadi et al., 2013) VSVg-pseudo-typed virus was used, the receptor and co-receptor binding, the fusion and uncoating parameters are not relevant to the *in vivo* HIV infection. We therefore developed a simplified ODE model (Fig. S1) to account for the experimental measurement and derive the useful parameters for the SST model.

$$\frac{dV}{dt} = \theta_1 \cdot \theta_2 \cdot e^{-\theta_2 t} - \theta_{11} \cdot V \tag{1}$$

$$\frac{dERT}{dt} = \theta_{11} \cdot V - \theta_3 \cdot ERT \tag{2}$$

$$\frac{dD}{dt} = \theta_3 \cdot ERT(t-\theta_{12}) - (\theta_4+\theta_5+\theta_6+\theta_7) \cdot D \tag{3}$$

$$\frac{dL_1}{dt} = \theta_7 \cdot D - \theta_8 \cdot L_1 \tag{4}$$

$$\frac{dL_2}{dt} = \theta_6 \cdot D - \theta_9 \cdot L_2 \tag{5}$$

$$\frac{dI}{dt} = \theta_5 \cdot D - \theta_{10} \cdot I \tag{6}$$

In this model, V is the virion concentration inside the cell; ERT-early reversible transcription product, D-linear cDNA, L1–1 LTR circle; L2–2LTR circle. I – integrated provirion.

The virion internalization is assumed to be a first order process with rate constant θ_2 and the initial virus concentration in the media is θ_1. Then the outside virion concentration V_o can be described by ODE: $dVo/dt = -\theta_2 V_o$ with initial concentration θ_1. So $V_o = \theta_1 \ exp(-\theta_2 t)$, and the internalization flux in Eq. (1): $\theta_2 V_o = \theta_1 \theta_2 \ exp(-\theta_2 t)$. The full description of the parameters in the model can be found in Fig. S1C. The experimental data (Fig. 1A and Fig. S2 from (Mohammadi et al., 2013)) were measured by qPCR and normalized to each species' own specific value at 24 h. To match such kinds experimental data, scaling parameters have to be introduced in the model (see θ_{13-16} in Fig. S1C).

To fit the experimental data, we used RMSD between simulation and data as the objective function and employed nonlinear least-squares solver -'lsqnonlin' function from Matlab to run the optimization. As 'lsqnonlin' can only find the local minimum, we supplied it with 10^6 initial parameter values in the parameter space (10^{-2} to 10^2 for non-scale parameters and 10^{-5} to 10^{-1} for the scaling parameter). We recorded the best solution and the 95% confidence interval for each parameter defined by the boundary of changing RMSD 5% as well.

2.2. The SST model

The model diagram and reactions are shown in Fig. 1A and Table 1. The model consists of three parts. The first part includes binding and unbinding to the CD4 receptor and co-receptor (CCR5 in this study),

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