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Mathematical models of viral latency

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While viral latency remains one of the biggest challenges for successful antiviral therapy, it has also inspired mathematical modelers to develop dynamical system approaches with the aim of predicting the impact of drug efficacy on disease progression and the persistence of latent viral reservoirs. In this review we present several differential equation models and assess their relative success in giving advice to the working clinician and their predictive power for inferring long term viral eradication from short term abatement. Many models predict that there is a considerable likelihood of viral rebound due to continuous reseeding of latent reservoirs. Most mathematical models of HIV latency suffer from being reductionist by ignoring the growing variety of different cell types harboring latent virus, the considerable intercellular delay involved in reactivation, and host-related epigenetic modifications which may alter considerably the dynamical system of immune cell populations.

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Introduction

Viral latency is a reversible state of nonproductively infected host cells [1]. Once integrated in the nucleus of the cell, the virus may remain dormant; that is, for certain time periods no new virions are produced, but nevertheless the inactivated viral genome remains potentially harmful by virtue of host cell proliferation. For the case of proviral latency, cytokine induction can activate the virus from its dormant state [2] such that the provirus enters the lytic infection cycle. Besides escape mutations during the early infection phase [3–5], viral latency constitutes a major challenge for both efficient drug treatment and mathematical modeling of infectious disease. In the present review we discuss mathematical models that predict the size of viral reservoirs evolving during the course of infection and their capability of producing rebounds of viral load. We highlight the use of differential equations (e.g. [6–9,10••,11]) which have proven to most successfully model the temporal dynamics of molecular factors involved with latent viral infection. Such models aim to make accurate predictions about the efficacy of treatment administration.

Given the possibilities of deep sequencing [12] and the better understanding of epigenetic factors involved in latency [13], we also touch on new directions of modeling the interplay of host-related epigenetic regulation and evolving latent reservoirs in the context of therapy design.

Basic differential equations models of HIV latency

Being the most prominent example of proviral latency, we discuss in detail modeling approaches for HIV latency (see Figure 1). The main reservoirs of latent HIV are memory CD4$^+$ T lymphocytes which harbor integrated proviruses that are unable to complete their lifecycle [14]. Model compartments are given by the variables T, L, T^* and V: the number of susceptible, latently infected and effectively infected CD4$^+$ lymphocytes and viral load in blood serum, respectively.

On the left-hand side of Eqn 1–4 (see [10••,15] for model parameters) there appear change rates of the variables defined by $(dT^*/dt)(s) \approx (T^*(s+\Delta) - T^*(s))/\Delta$ for a short time increment $\Delta > 0$. On the right-hand side the so-called incidence function F determines the interdependence of T cell and viral populations and their presumed effect on the rate of change of T, T^* and L (see Figure 2). All variables are dependent upon time s, which is omitted for notational convenience:

$$\frac{dT}{dt} = \alpha - F(T,V) - d_T T \quad (1)$$

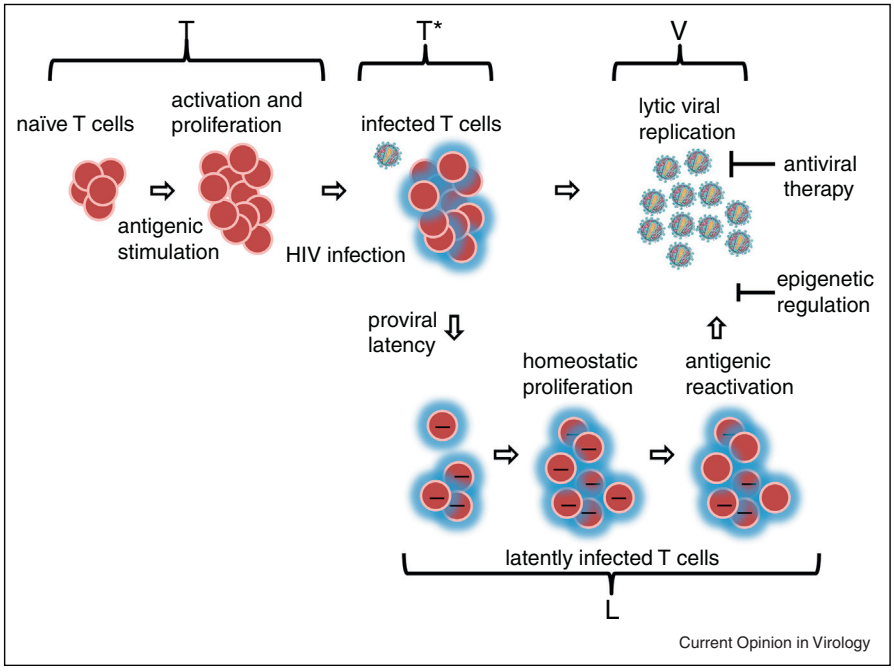
$$\frac{dL}{dt} = \eta(1-\varepsilon)F(T,V) - d_L L - a_L L \quad (2)$$

$$\frac{dT^*}{dt} = (1-\eta)\varepsilon F(T,V) - d_{T^*} T^* - a_L L \quad (3)$$

$$\frac{dV}{dt} = pT^* - cV \quad (4)$$

The model parameters are the recruitment rate of susceptible T cells, α the rate of transition from latently infected to productively infected cells a_L, the cell death

Figure 1



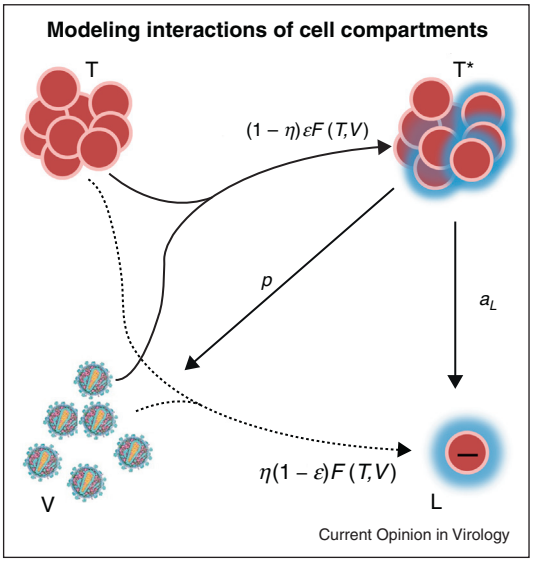
Basic cell compartments involved with HIV infection: susceptible T cells (*T*), effectively infected T cells (*T**), latently infected T cells (*L*) and viremia due to lytic viral replication (*V*).

rates d_T, d_L and d_{T^*}, the drug efficacy ε, the fraction of infection η leading to proviral latency, the viral clearance rate c, and the virus production rate p. As an example we discuss Eqn 2:

The incremental change of the latent viral reservoir dL/dT is given by the product of viremia and susceptible T cells, which means that assuming constant viremia, the latent reservoir changes in linear dependence according to the number of susceptible T cells. η being usually 10^{-3} [16], only a few susceptible cells become latently infected, the majority $1-\eta$ being effectively infected. Drug efficacy ε is set around 0.85, but since provirus is neither affected by protease inhibition nor by antiretroviral drugs, it is the inefficacy rate $1-\varepsilon$ that affects the change rate of the latent reservoir. Antigen presentation may reactivate latent provirus such that $a_L = 0.1$ latently infected cells leave the reservoir. Memory $CD4^+$ T cells also undergo apoptosis with constant rate $d_L = 10^{-3}$.

***F*(*T*,*V*) = 1**: Linear equations assume that the change rate of plasma viremia and $CD4^+$ T cells within a small amount of time is proportional to their starting concentration. In [17] it is shown that such a model can explain a rebound of viral load despite a long period of declining virus production. Because the pool of dormant virus has considerable genomic variety [18], it is necessary to introduce a continuous range of activation rates for the provirus depending on the particular strain. Accessory cells (such as macrophages) which are specific for rare antigens have thus lower probability of being activated and the mathematical model predicts a decelerating decay of latently infected cells upon highly active antiretroviral therapy (HAART).

Figure 2



The incidence function $F(T,V)$ quantifies to which extent the size of susceptible T cell populations and viremia lead to reactivation.