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Excitability in the host–pathogen interactions of HIV infection and emergence of viral load blips

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HIGHLIGHTS

- We modeled the dynamic HIV infection to interpret the emergence of viral blips.
- HIV host–pathogen interactions are shown to be excitable under adequate conditions.
- In these conditions, viral-pool perturbations are shown to efficiently trigger viral blips.
- Perturbations of CD4 and CD8 T-cell density are shown to trigger blips but to a lesser extent.
- Blips are of low clinical significance as any viraemia perturbation could trigger them.

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ABSTRACT

HIV viral blips are characterized by intermittent episodes of detectable low-level viraemia which return spontaneously to an undetectable level in patients with full suppression of viraemia (<50 copies/ml). The precise mechanisms responsible for viraemia blips and their clinical significance are not known. In this work, we analyze HIV blips using a mathematical model describing basic host–pathogen interactions, in particular regulatory processes involving CD4+, CD8+ T-cells and the virus. We show that under adequate conditions, this interaction system can be excitable and small perturbations of the system by external stimuli can generate robust viral load (VL) blips of regular or irregular frequency and peak amplitudes. Importantly, our analysis showed that direct perturbations of the viral load (by latent reservoirs or opportunistic diseases for example) more efficiently trigger VL blips on contrary to direct perturbations of the immune system, in particular the levels of uninfected CD4+ and cytotoxic CD8+ T-cells. This feature is shown to rely on specific stability properties in this interaction system. Our analysis moreover suggests that blips should be of low clinical significance since any other VL or immune system perturbations could trigger transient viraemia under adequate excitability conditions.

1. Introduction

HIV-infected patients require a lifetime therapy since the virus cannot be eradicated to date. Highly active antiretroviral therapies, based on two or more classes of treatments (e.g. protease and reverse transcriptase inhibitors), enable to decrease the viral load (VL) below the detectability level of 50 copies/ml after few weeks or few months of treatment (Ouattara et al., 2008). When the treatment is efficient, patients can show a sustained low VL during several months or years (Nowak and May, 2000; Jeffrey et al., 2005). However, a number of them often experiences intermittent transient viraemia (above the detectability level) also called viral blips (Lee et al., 2006). The precise mechanisms responsible for viral blips are not well understood. Several studies reported that these viral episodes could be associated with virological failures (Raboud et al., 2002), drug resistances (Macias et al., 2005; Stuart et al., 2001), while others showed that they are clinically insignificant and rather represent random variations of the VL around mean levels below the detectability level (Nettles et al., 2005; Lee et al., 2006).

Several mathematical models were therefore proposed to describe and interpret VL blips. Jones and Perelson (2005) suggested that latent reservoirs could be responsible for viral blips by producing new virus when stimulated by relevant antigens. The model was in agreement with the data of Chun et al. (1998) who showed that

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in vitro combinations of the pro-inflammatory cytokine interleukin (IL)-6 and tumour necrosis factor (TNF)-alpha and the immunoregulatory cytokine IL-2 are potent inducers of viral replication and latently reservoirs replenishment, suggesting their implication in viral blips. Other similar models were proposed by Rong and Perelson (2009a,b). Using a simpler model, Ouifki and Witten (2009) showed that basic interactions between healthy CD4+ T-cells, infected CD4+ T-cells and HIV can exhibit oscillations through a Hopf bifurcation point, suggesting that this simple model may provide an interpretation of HIV blips. However, because HIV blips cannot be explained by periodic HIV peaks alone, other factors should be considered in the model to reliably interpret blips.

Cytotoxic CD8+ T-cells are important for the immune control of HIV although the mechanisms of this control are unclear (Davenport and Petravic, 2010). Using simian immunodeficiency virus (SIV)-infected macaques, several studies reported that the rate of decay of productively infected cells was not altered by cytotoxic CD8+ T cells (Klatt et al., 2010; Wong et al., 2010; Balamurali et al., 2010), despite strong evidences of VL increase in CD8+ T cells-depleted individuals (Wong et al., 2010; Okoye et al., 2009). However, direct killing of productively infected cells by cytotoxic T lymphocytes (CTL or cytotoxic CD8+ T-cells) was early reported by Nixon et al. (1988), Tsubota et al. (1989) and more recently by Migueles et al. (2008) and Sáez-Cirión et al. (2007, 2009). This lytic function of cytotoxic T lymphocytes was moreover suggested to play a pivotal role in long term non-progressors and in HIV controllers (Migueles et al., 2008; Sáez-Cirión et al., 2007, 2009).

In this paper, we analyze HIV blips using a mathematical model describing host–pathogen interactions, in particular regulatory processes between CD4+ T-cells, CD8+ T-cells and the virus. Because VL blips are unpredictable, transient and suggested to be induced by external stimulation of the VL, they strongly resemble self-induced stochastic resonance (or perturbation-induced pulses) occurring in excitable dynamical systems. Excitable systems consist of a set of coupled excitatory and recovery variables with large-time scale separations (Muratov et al., 2005). Excitatory variables are involved in fast-response auto-catalytic regulatory processes (i.e. positive feedback loops) and generate pulses while recovery variables are slow dynamics that cause the system to return to its resting state. In the frame of HIV infection, basic host–pathogen interactions can be separated in two cross-regulated modules. A fast-kinetic module consisting in the auto-catalytic loop between productively infected cells and virus and a slow-kinetic module consisting in a negative feedback loop between productively infected CD4+ T cells and cytotoxic CD8+ T cells (Fig. 1). We therefore asked whether these feedback circuits and time-scale separations in the HIV infection system could generate excitability and perturbation-induced blips of the VL. The mathematical model we used involves basic interactions between two key actors of the immune system, CD4+ and CD8+ T cells, and the virus. It was shown that this simple system can be excitable and excitability only relies on intrinsic host–pathogen interactions between virus, CD4+ and CD8+ T cells. However, under excitability conditions, internal fluctuations emerging from these intrinsic interactions, were shown to be insufficient to trigger VL blips. On the contrary, external perturbations that can be associated with other biological processes such as latent reservoirs, antigenic stimuli or co-infections were shown to be essential for the emergence of VL blips. This work therefore reinforces the need to account for these non-modelled compartments for a good interpretation of HIV/AIDS dynamics.

2. The mathematical model

The model describes basic biological interactions between the virus and the healthy CD4+ T cells, the infected CD4+ T cells and CD8+ T-cells (Fig. 1), and is given as follows:

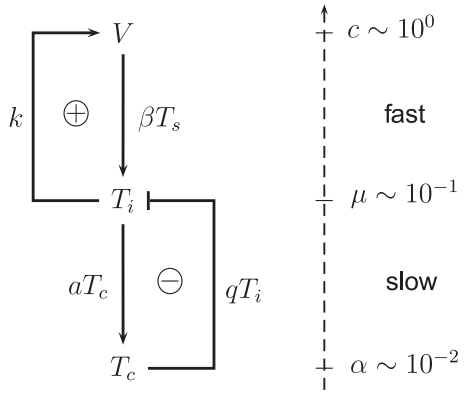

Fig. 1. Host–pathogen interactions involved in HIV infection. Normal and blunt arrows correspond to positive and negative interactions, respectively. T_s, T_i T_c, V are uninfected and infected CD4+ T cells, CD8+ T cells and virus, respectively. Variable time scales are given by their half-lives on the right side. Parameters are described in Table 1. Slow recovery variables (T_s, T_c) are coupled with fast excitatory variables (T_i, V) through a negative and positive feedback loop. Loop signs are given by "+" and "−" into circles.

$$\frac{dT_s}{dt} = s - \delta T_s - \beta T_s V$$

$$\frac{dT_i}{dt} = \beta T_s V - \mu T_i - q T_i T_c$$

$$\frac{dT_c}{dt} = \lambda + a T_i T_c - \alpha T_c$$

$$\frac{dV}{dt} = k T_i - \beta T_s V - cV. \quad (1)$$

In this four-variable model, say model Σ_{4D}, free virions infect healthy CD4+ T cells at a rate βTV proportional to the VL (V, RNA copies/ml) and the density of healthy CD4+ T-cells (T_s, CD4/mm^3). Productively infected CD4+ T cells (T_i, CD4/mm^3) produce new virions at a rate kT_i and are eliminated by CD8+ T cells at a rate qT_iT_c proportional to the density of infected cells and cytotoxic T lymphocytes (T_c, CD8/mm^3). Parameters δ, μ, α and c are the natural death rates of healthy CD4+ T cells, infected CD4+ T cells, CD8+ T cells and virus, respectively. In our model, we also assumed that cytotoxic T lymphocytes proliferate at a rate aT_iT_c proportional to the density of CD8+, and infected CD4+ T cells. Although CD8+ T cells may alternatively regulate VL through different mechanisms (Klatt et al., 2010; Wong et al., 2010; Balamurali et al., 2010), we only considered their cytolytic regulatory activity that is documented (Migueles et al., 2008; Sáez-Cirión et al., 2007, 2009) and well modelled in literature (e.g. Wodarz et al., 2000). To have a biologically relevant model, we further assumed basal production rates for CD4+ and CD8+ T-cells that are modeled through parameters s and λ. All the parameters of the model are described in Table 1.

We aimed here at modelling basic interactions between the key actors of the infection process while keeping a rather simple mathematical description (Fig. 1). Of note, several aspects of the infection are not considered, in particular CD4+ and CD8+ T-cell apoptosis (Ahr et al., 2004; Mhawej et al., 2009; Moon and Yang, 2006; Stan et al., 2008) and proliferation, macrophage interactions with HIV (Capistrán, 2010; Mahlknecht and Herbein, 2001), latent reservoirs dynamics (Capistrán, 2010; Rong and Perelson, 2009b) or viral resistance.