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# Modelling the HIV persistence through the network of lymphocyte recirculation in vivo

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ABSTRACT

Human Immunodeficiency Virus (HIV) is able to persist in cellular and/or anatomical viral reservoirs, despite the effective inhibition of virus replication by the antiretroviral therapy (ART). Here we develop a mathematical model to gain some insights of HIV persistence relevant to the lymphocyte recirculation network of immune system and the central nervous system (CNS). Our simulations and analyses illustrate the role of the CNS as a virus reservoir to prevent antiretroviral drugs from penetrating the blood-brain (or blood-testis) barrier, and we examine the long-term impact of this reservoir on the transmissibility of an infected individual. We observe numerically that level of HIV in peripheral blood may not accurately reflect the true mechanisms occurring within other organs.


## 1. Introduction

### 1.1. The immune system and lymphocyte recirculation

The immune system protects the human body against diseases or any potentially threatening foreign bodies (e.g., virus, bacteria and parasites). The immune system operates throughout the body. However, there are certain sites where the cells of the immune system are organized with specific structures, classified as the central lymphoid tissue (e.g., bone marrow, thymus) and peripheral lymphoid tissues (e.g., lymph nodes, spleen, mucosa-associated lymphoid tissue). There are about 600–700 lymph nodes present in the human body. Lymphocytes can recirculate between lymphoid and non-lymphoid tissues, which allows lymphocytes to fight against antigens. The lymphocytes is valuable in distributing effector cells among sites where they are needed. The recirculation is a complex process as shown in (Sae-Jang, ), where recirculation involves the procedure of a precursor pool of uncommitted lymphocytes from the blood into lymph nodes or mucosal lymphatic tissues and then moves back to the blood again, forming the basis of immuno-surveillance and integration of immune functions across the segregated systems. Activated lymphocytes move from the spleen and lymph nodes into the

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blood as well as other lymphoid and non-lymphoid tissues. Enough lymphocytes recirculation from the lymph to blood can replace the total blood lymphocyte pool from 10 to 48 times every 24 h.

### 1.2. HIV in blood, tissues and reservoirs

Persistent low-level viremia is a common feature among HIV patients treated with highly active antiretroviral therapy (HAART) (Levy, 1995). An important research question to address is whether residual viremia can lead to ongoing cycles of viral replication even under HAART, or it signifies a release of virus from stable reservoirs infected before the initiation of therapy. Several reports have shown that no viral evolution happened among treated patients (Bailey et al., 2006; Nottet et al., 2009; Persaud et al., 2004), indicating that ART can completely stop viral replication at least among some patients (Shen & Siliciano, 2008). In a study among patients who discontinued drugs during the structured treatment interruptions (STI) therapy, these rebounding virus resembled pretreatment virus, and did not show any evidence of genetic evolution over time (Joos et al., 2008). The lack of new resistance mutations detected in patients on ART with suppressed plasma viremia (less than 50 copies/ml) further argues against ongoing viral replication, implying the release of virus from stable cellular reservoirs as an important source for residual viremia (Nettles et al., 2005; Nottet et al., 2009; Persaud et al., 2004). Virus isolated from resting memory $CD4^+$ T-cells has been shown to be closely related to residual plasma virus that found among patients with ongoing ART, thus indicating the latent reservoir as a source of residual viremia in these patients (Bailey et al., 2006; Nottet et al., 2009; Persaud et al., 2004; Shen & Siliciano, 2008). Latently infected resting memory $CD4^+$ T-cells can persist for years (half-life, 44 months), which represent a major barrier to HIV eradication. Removal of HIV from these resting memory $CD4^+$ T-cells or other reservoirs of other tissues (e.g., the brain) could take considerably longer or even be unattainable (Levy, 1995).

HIV virions are produced by infected cells in both lymphoid tissues and blood (Haase et al., 1996; Perelson et al., 1997). Because of a great concern for the reported HIV transmission by blood, major efforts have been made earlier to quantify the amount of virus in blood. The results indicated that both freely-flowed virus and infected cells were present in blood regardless if the HIV-infected individual is asymptomatic or develops AIDS (Levy, 1995). However, in many cases, the level of freely-flowed virus in the peripheral blood, even following antiviral therapy, may not give an accurate reflection of what is occurring within the body (Levy, 1995). For instance, the study (Ping et al., 2000) reported that the quantity of HIV in blood plasma may not reflect the level of semen viremia. Researchers (Tachet et al., 1999) also found a small group of men had RNA levels in seminal plasma comparable to or even higher than that detected in blood plasma (Levy, 1995). Other literature also revealed that virus can be detected in semen by cell culture or PCR techniques despite antiviral therapy when plasma virus levels were low or undetectable (Hamed, Winters, Holodniy, Katzenstein, & Merigan, 1993; Vernazza et al., 1994). These findings indicate the inability of some drugs to penetrate the blood-testis barrier and emphasize the transmissibility of an infected person despite low viremia levels (Barker & Billingham, 1997; Levy, 1995).

Like what has happened in testis, HIV has also been readily isolated, even in early infection, from the central nervous system (CNS). About a quarter of AIDS patients have neurologic symptoms, particularly the HIV encephalitis, which can occur despite the use of HAART (Levy, 1995). In contrast to these body fluids, cerebrospinal fluid (CSF) contains large amounts of virus, particularly in individuals with neurologic findings. It can be present in the CSF of asymptomatic individuals (Ho et al., 1985; Levy, 1995; Levy, Hollander, Shimabukuro, Mills, & Kaminsky, 1985). Simultaneous comparison of viral RNA sequences in CSF and plasma samples have indicated that the differences that support the conclusion that the brain is a distinct compartment particularly within the choroid plexus (Burkala, He, West, Wood, & Petito, 2005; Tang, Huong, Lloyd, Spearman, & Haas, 2000). The mechanism(s) by which HIV enters the CNS is not known, but entry occurs obviously among freely-flowed virus or among infected cells. Activated infected cells enter the CNS by attachment and diapedesis between endothelial cells (Hickey, Hsu, & Kimura, 1991). Both types of peripheral blood cells (macrophages and $CD4^+$ T-cells) could, therefore, be the initial source of HIV infection, although in vitro studies suggest that infected CD4 lymphocytes preferentially migrate to the brain through the endothelium (Birdsall et al., 1997). Similarly, freely-flowed virus can readily enter the CSF and brain from the blood via the vascular endothelium (Davis et al., 1992).

## 2. The model

Insights into HIV dynamics in vivo have been obtained from mathematical modelling (see e.g., (Nowak & May 2001; Perelson & Nelson, 1999)). Competition models have been formulated in the context of the dynamics of virus-host interactions in the past two decades (Frost & McLean, 1994; Korthals Altes and.Jansen, 2000; McLean & Nowak, 1992; Rong, Feng, & Perelson, 2007; Smith & Wahl, 2004, 2005; Wahl & Nowak, 2000). These models embedded the knowledge on the possible dynamics of HIV-1 infection into relatively complex systems of non-linear differential equations. Such results can be used, for example, to investigate different hypotheses on HIV dynamics through numerical simulations. In (Callaway & Perelson, 2002) authors examined the predictability of several biologically oriented models of HIV-1 dynamics to explain sustained low viral loads. They built a chronically infected cell model by considering the infection stages occurring in two distinct compartments, with one regarded as a drug sanctuary, such as the brain, or testis. These compartments are then coupled by allowing the transportation of virus between these compartments. Authors permitted virus transporting between the main compartment and the sanctuary. Considering the lymphocyte recirculation, our model is a modified version of this