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Markov process models of the dynamics of HIV reservoirs

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ABSTRACT

While latently infected CD4+ T cells are extremely sparse, they are a reality that prevents HIV from being cured, and their dynamics are largely unknown. We begin with a two-state Markov process that models the outcomes of regular but infrequent blood tests for latently infected cells in an HIV positive patient under drug therapy. We then model the hidden dynamics of a latently infected CD4+ T cell in an HIV positive patient and show there is a limiting distribution, which indicates in which compartments the HIV typically can be found. Our model shows that the limiting distribution of latently infected cells reveals the presence of latency in every compartment with positive probability, supported by clinical data. We also show that the hidden Markov model determines the outcome of blood tests and analyze its connection to the blood test model.

1. Introduction

Up to now, eradicating the human immunodeficiency virus (HIV-1, which we denote by HIV) in an individual who has become infected has remained out of reach of current medical practice. However the advent of antiretroviral therapy (ART) changed HIV from a direct path to AIDS, a fatal disease, to a chronic disease [22,27,28]. As early as 1996 studies showed that even effective ART that brings the level of HIV below the level of detection in the blood does not successfully eliminate the virions from other cells or biological compartments in the body [7,13,21,26].

There remains a fundamental problem of understanding how and why the reservoirs are formed and maintained, and why the current drug therapy does not completely eradicate them. When ART is stopped, in all patients (with one possible exception known as the Berlin patient), the virus reappears in the blood after a period of time that varies from individual to individual [14], often as soon as a few weeks later [4]. In the case of the Berlin patient, he had developed acute myelogeneous leukemia, and was treated with a stem cell transplant from a donor harboring a mutated form of the CCR5 receptor that provides resistance to HIV infection. The patient's continued absence of detectable virions has led to exploration of a cure in this direction [32]. Another notable case is referred to as the "Mississippi baby" where HIV infection was discovered and treated within 2 days of birth, and ART was administered for about 18 months. After stopping the drug, the virus remained undetectable for 27 months, but viral rebound occurred [19].

We approach this topic by presenting two models of the location of latently infected cells, referred to as HIV reservoirs, in an individual undergoing ART, as Markov processes. These models utilize a tool in dynamical systems that is advantageous for analyzing spatiotemporal phenomena in extremely complex systems, even those systems whose dynamics are far from random, as is the case here. Instead of following each individual virus particle or infected cell, since there can be millions of virions detected per milliliter of blood in a newly infected or untreated patient, and since it has been shown to be impossible to track and destroy a single virus, or more importantly, every virus particle, we study qualitative and probabilistic aspects of the dynamics of HIV reservoirs. Moreover since typically a blood sample is used to determine the virus levels of a patient, the actual location of source of the virus remains hidden. Therefore we are in fact dealing with a hidden Markov model; that is, there is the output that is viewed (a blood test showing the presence or absence of virus) and a hidden process that is governing the output. Our models incorporate this multilevel structure.

There are several prevailing theories about why HIV has remained incurable so far; we mention a few here. First, the host cells for the virions are CD4+ T helper cells, white blood cells essential to a functioning immune system. Their main role is to signal other T cells to destroy pathogens. Once a CD4+ T cell becomes actively infected by HIV, the immune cell usually is destroyed; it can also happen that the HIV enters the cell and produces viral DNA but does not complete the replication process [6].

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While the drug therapy appears to inhibit the replication of virtually all active susceptible virions in the blood, there seem to be virions hiding outside the path of the drugs [10]. In one recent review on latency of the virus under drug therapy [6], the authors offer an opinion that the drugs are not able to go effectively to all sites where the virions can be found:

> Recent studies have indicated that anti-retroviral drug- penetration is site- and compound-specific, and drugs that penetrate poorly may allow viral replication at that site even when plasma viral load is below 50 copies ml^{-1}.

Such locations are called sanctuary sites but are not the subject of this study.

Another theory as to why cures (and vaccinations) remain inaccessible is that the virus is known to mutate extremely quickly. Autopsies of patients with HIV show numerous variations (species) of the virus exist in a body, even within a single organ [2]. This aspect of HIV dynamics is treated mathematically using cellular automata models first introduced in [34], and developed rigorously in [5]. In a follow-up paper by Hawkins and Molinek [18] the authors show that the model has limiting values of healthy CD4+ T cells that can occur and the viral particles are never completely eliminated without "perfect drugs" that are 100% effective in all compartments of the body, coupled with an immune response that can eradicate all the HIV. Up to now this has not been achieved.

In addition to the possibility of active replicating viruses perhaps even under drug therapy, albeit at a low level, it is now generally accepted that there are reservoirs of latent viruses that can persist in the system of an HIV infected patient for years [6,7,14], which form the focus of this paper. A working definition is that a latently infected cell is a cell that does not produce infectious viral particles but is able to do so at some future time, behaving like a Trojan horse. The cell appears to be a healthy cell to the immune system, the drugs do not affect the hidden virions, so it can spring to action at any moment with the viruses replicating in the host cell and producing millions of new virions. The passive viral material (provirus) is passed to cells during normal cellular replication and can reactivate without warning. Therefore up to now, killing the cell containing the provirus seems to be one of the only ways to get rid of the provirus [4]. Many studies have shown that there remain latently infected resting CD4+ T cells in the lymph nodes and other organs; moreover these reservoirs can be long-lived, with a mean half-life of more than 3 years [13]. A clinical study of 36 HIV patients on ART showed the presence of viruses able to replicate in 34 of the patients, with a typical occurrence of .1 - 1.0 infectious units per million resting CD4+ T cells [13].

To summarize, while ART is effective in suppressing HIV replication indefinitely, it does not eradicate all the virions in the system and HIV seems to return in virtually all patients, and sometimes quite quickly when treatment is stopped. The reason for the term "HIV reservoir" is that the genome of the virus is securely protected by a seemingly healthy cell until something activates it to continue to HIV production. While the definition of reservoir has other interpretations, evidence shows this is the most likely so we use that here [12] and do not work with sanctuary sites, except indirectly. We make some simplifying assumptions throughout; one is that the latently infected cells are CD4+ T cells, even though there is evidence that other types of cells may serve as reservoirs for HIV [1]. The other assumption is that latently infected CD4+ T cells circulate, though our model allows for the existence of resident cells as well [25]. This is discussed in Section 2.3.

In this paper we construct a mathematical model based on limited data about the reservoirs that have been observed and analyzed in clinical studies. The virions, as well as most actively and latently infected cells circulate throughout the body through biological pathways, and the location of a latently infected cell at any given moment is extremely complex. While most studies indicate that CD4+ T cells circulate throughout a body, we incorporate the observation that some CD4+ T cells remain resident in certain locations [24,25]. Our use of stochastic methods to understand and model the location of the latently infected cells, and how they impact a blood test, does not assume that the migration of the cells is random. Indeed the movement of T cells throughout a body is subject to severe physical stresses (fast blood flow) as well as pressure to remain near lymph nodes. Our model uses the stochastic features of the movement, bolstered by some theorems that estimate the rate of spread, and the limiting distributions. We conclude that after a fairly short period of time (perhaps measured in days), latently infected cells have spread sparsely throughout the body. This indicates that treatment ought to follow the same pathways and dynamical processes in order to reach the hidden virus.

We introduce and analyze the mathematical models in Sections 2.1 and 2.3. We give a simple two-state Markov process model of the outcome of blood tests for the presence of viral particles in Sec. 2.1, and in Sec. 2.3 we show the existence of a hidden Markov model that more accurately reflects the dynamics of the latently infected cells, and show it is a lifting of the two-state model. In Section 2.2 we give an overview of the location of the reservoirs based on the scientific literature. In Section 3 we assign some specific sample numbers to the entries in the matrices and compare the resulting measures on both models.

2. Theory and Models

2.1. The two-state model

When a blood sample is taken from an HIV positive patient under drug treatment, it is expected that the viral presence will be below the detectable levels [3,8]. More elaborate tests can be performed to assess the presence of latently infected CD4+ T cells [3,8] in the blood, however there is no simple method for measuring the presence and level of latently infected cells [16]. Therefore, after each sample is tested, we can think of the blood as being in one of two states, either the test is positive for the presence of such cells (state $P = 1$) or negative (state $N = 0$). We assume this test is performed once a month and the outcome is recorded. We also assume the blood is sampled monthly for an indefinite period of time, and we construct a Markov chain from the results.

This yields the following 2×2 incidence matrix B, where $b_{ij} = 1$ if and only if you can get from state i to state j in one time step. Clearly a negative test can be followed by a positive one, and the same result can occur twice in a row; our assumption is that once the presence of latently infected CD4+ T cells is established with a positive blood test result, the latently infected cells cannot be destroyed easily though the blood test could come back negative if the quantity of latently infected cells, believed to be very sparse, is not seen on a subsequent test. The adjacency graph in Figure 1 shows the possible connections between the nodes of Positive and Negative; even though the likelihood of each arrow is different (as shown in (2.2)), the graph shows it is possible for each blood test outcome to be followed by either outcome.

$$B = \begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix} \tag{2.1}$$

The matrix is equivalent to the directed graph in Fig. 1, where $B = b_{ij}$, and $b_{ij} = 1$ if and only if there is an arrow from state i to j and 0 otherwise.

We start with a simple one-step Markov process associated to B; we review the mathematical underpinnings of a Markov process first. We begin with the space of all possible infinite sequences of outcomes, $\Omega = \{0, 1\}^{\mathbb{N}}$; a point $x \in \Omega$ is a one-sided sequence of

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