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Physica A ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at SciVerse ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Cellular automata approach for the dynamics of HIV infection under antiretrovial therapies: The role of the virus diffusion

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ARTICLE INFO

Article history:
Received 7 August 2012
Available online xxxx

Keywords:
Cellular automata
HIV infection
Self-adjusted effectiveness
Virus diffusion

ABSTRACT

We study a cellular automata model to test the timing of antiretroviral therapy strategies for the dynamics of infection with human immunodeficiency virus (HIV). We focus on the role of virus diffusion when its population is included in previous cellular automata model that describes the dynamics of the lymphocytes cells population during infection. This inclusion allows us to consider the spread of infection by the virus-cell interaction, beyond that which occurs by cell–cell contagion. The results show an acceleration of the infectious process in the absence of treatment, but show better efficiency in reducing the risk of the onset of AIDS when combined antiretroviral therapies are used even with drugs of low effectiveness. Comparison of results with clinical data supports the conclusions of this study.

1. Introduction

The treatment of combined antiretroviral therapies (cART), although it has not led to a cure, has succeeded in decreased mortality caused by AIDS and the prolonged life of HIV-infected patients since the end of the 90s [1]. Despite the great effort expended by physicians, biologists, immunologists, etc., the mechanisms which provide the permanence of the virus over long time scales (of the order of years) after primary infection (of the order of weeks), weakening the immune system and leading to AIDS remains the central point in the fighting of such a disease.

One of the important issues currently under discussion, is the moment of initiation and duration of treatment, which affect the results and costs of these therapies [2].

HIV infects T cells, macrophages and dendritic cells which are essential to the human immune system response, such as the $CD4^+$ T cells. As a retrovirus, its ribonucleic acid (RNA) is replicated within the cell by a process called enzyme reverse transcriptase (RT) to produce its DNA, which is incorporated into the host genome by a process called enzyme integrase. During its life cycle inside the cell new particles are produced and released continuing to infect other cells and in that way the infection spreads in the organism [3].

In general, the clinical course of HIV infection is monitored by changes in viral load and counting of $CD4^+$ T cells in the blood. This evolution contains three phases: the primary infection (timescale of the order of weeks), the period of clinical latency (timescale of the order of years) and the onset of AIDS which occurs when $CD4^+$ T counts decrease below the threshold of 200 cells per μL [4–6]. Below this threshold the adaptive immune response becomes deficient allowing the development of other fatal diseases.

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doi:10.1016/j.physa.2012.10.036

In this study, a cellular automata model (CA) is used to investigate the population dynamics of free viral particles and lymphocytes in an infection process under action of combined antiretroviral therapies. A detailed study of the corresponding dynamics of the $CD4^+$ T cell population under such treatment will be presented elsewhere.

The combined antiretroviral therapies (hereafter referred as cART) involve the use of two or more classes of antiretroviral drugs. Usually it consists of two reverse transcriptase inhibitors (RTI) plus a protease inhibitor (PI), which inhibit different vital functions of the HIV, the efforts being centered mainly in the blockade of two specific enzymes, that of reverse transcriptase (RT) and protease (P) [7–12]. In the present study we consider the action of these two classes of drugs, whether acting individually or in combination.

The present CA model is based on the original model proposed in Ref. [13], which was extended to include the viral population and the required mechanisms to describe the antiretroviral therapies. To describe the evolution of the populations of $CD4^+$ T cells and viruses, we consider two superimposed square lattices $L \times L$, each operating in its own timescale, corresponding to the timescale of cells and virus in a real infection. This interplay takes into account the virus–cell process of infection, the mechanism of production of new viral particles and their dispersion in the environment. Regarding the action of cART three new states are defined for healthy cells to consider cases in which they can absorb one of two classes of drugs or both, as originally proposed in Ref. [14]. We also add a mechanism to account for the variation in the effectiveness of the therapy caused the high mutation rate observed in the process of HIV replication. Such a mechanism ensures that the effectiveness of the drug varies in a self-adjusted way during the infection process, i.e. they have their maximum value at baseline evolving according to the density value of infected cells at each time instant.

In the following section we present a brief review of mathematical efforts made to describe the dynamics of HIV infection emphasizing the use of cellular automata models and presenting the CA model used here. In Section 3, the results for the dynamics of viral load under therapy are discussed and conclusions drawn.

2. Mathematical modeling for HIV dynamics

Since the discovery of HIV in the '80s and the appearance of the first therapies, mathematical models have been to describe certain aspects of the dynamics of infection and to test hypotheses for the persistence of HIV. In most cases, these models were formulated based on systems of coupled ordinary differential equations, which describe the rates of change of the average populations of cells and viruses involved in the process. For an intuitive introduction on the basic elements and concepts involved in modeling the dynamics of HIV and other viruses and their interactions with the immune system, the text by Nowak and May [15] is mainly indicated, while the one from Perelson and Nelson [16] is recommended for a review of mathematical models formulated during the 90s. Over the past decade, with the development of potent antiretroviral therapies, the models have become more complex and sophisticated in order to include new types of cells that participate in the immune response (e.g. Refs. [17–19]) and to consider their interactions with free virions, reverse transcriptase inhibiting drugs and protease inhibiting drugs [14].

Cellular automata models have also been proposed for this purpose as an approach for considering spatial-structured models, which have shown to be efficient with significant potential for describing the spatial and temporal dynamics of HIV. For instance, the CA model proposed in Ref. [13] was conceived to describe the course of HIV infection, through the behavior of the population of T cells in lymph nodes. The set of rules governing the dynamics of such a CA model were designed to test whether the combination of a healthy immune system with a high rate of viral mutation and a fair spatial localization of infected cells in lymph nodes, could describe the entire course of infection. Its results reproduce qualitatively well the three time scales of the phases of HIV dynamics (primary infection, clinical latency and onset of AIDS). It also inspired other CA models with the aim to investigate related aspects of HIV infection and to include the processes of antiretroviral therapy [20–25].

In the present model, $CD4^+$ T cells are fixed and arranged in a square lattice, representing the environment of a lymph node according to Ref. [13], while the virus population can diffuse across the superimposed lattice following rules that simulate the process infection of the cell and release of new viral particles replicated inside the infected cells.

The following subsections describe in detail the states of cellular automata, the mechanism that controls the self-adjusted effectiveness, and finally present the rules of the dynamics of the model.

2.1. States of the automata

The states of cellular automata in the network of cells before treatment is initiated corresponds to that defined in Ref. [13], which are:

H: susceptible uninfected healthy cells.
A_1: productive infected cells that have not been identified by the immune system and possess greater power of infection.
A_2: productive infected cells already detected by the immune system and possess less power of infection than the A_1 cells.
D: dead cells.

From the beginning of treatment, the H state of healthy cells is replaced by four possible states in accordance with the respective absorption of drug, as proposed in Ref. [14], namely:

H: healthy cell that did not absorb any drug.
H_{RT}: healthy cell that absorbed reverse transcriptase inhibitor.

Please cite this article in press as: R.E.R. González, et al., Cellular automata approach for the dynamics of HIV infection under antiretrovial therapies: The role of the virus diffusion, Physica A (2012), doi:10.1016/j.physa.2012.10.036