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Statistical behavior of time dynamics evolution of HIV infection

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ABSTRACT

We use the tools of the random matrix theory (RMT) to investigate the statistical behavior of the evolution of human immunodeficiency virus (HIV) infection. By means of the nearest-neighbor spacing distribution we have identified four distinct regimes of the evolution of HIV infection. We verified that at the beginning of the so-called clinical latency phase the concentration of infected cells grows slowly and evolves in a correlated way. This regime is followed by another one in which the correlation is lost and that in turn leads the system to a regime in which the increase of infected cells is faster and correlated. In the final phase, the one in which acquired immunodeficiency syndrome (AIDS) is stablished, the system presents maximum correlation as demonstrated by GOE distribution.

1. Introduction

Since the first cases of human immunodeficiency virus (HIV) infection were diagnosed many investigations have been carried out in order to understand the evolution of the infection [1–6]. The dynamics of HIV infection is characterized by three distinct phases which are related to the evolution of the degree of infectability. In the first one, the primary infection, a peak in the infection level is observed around 5 weeks after the contagion. This phase lasts from 10 to 12 weeks. After this period the immune system presents false signs of recovery. The second phase, the clinical latency period, is characterized by a very low viral concentration followed by a gradual growth which leads to the impairment of essential functions of the immune system. This period may last for 2 to 10 years. After this period the probability of the patient developing acquired immunodeficiency syndrome (AIDS) is very large.

Several mathematical models have been proposed to study the dynamics of HIV infection [4]. Most of the investigations are based on the use of differential equations but models in which the spatial structure is considered have also been developed. In this sense, Zorzenon dos Santos and Coutinho [1] used a cellular automata model to study the evolution of HIV infection and the onset of AIDS. Their model propose a local interaction among the different types of cells (healthy, infected and dead), while the lymph node is modeled by using a square lattice with periodic boundary conditions and Moore neighborhood. The model was able to reproduce the time scales of the three phases of the infection.

The random matrix theory (RMT) was proposed by Wigner and Dyson for the study of the statistical properties of the spectrum of complex nuclei [7,8]. This approach has been successfully applied to the study of many subjects such as wireless communications [9], chaotic systems [10], protein dynamics [11,12] and structure and interactions of biological networks [13]. Furthermore, the RMT can also be applied to multivariate time series as electroencephalographic recordings with epileptic events [14] and financial time series [15,16], which motivated us using this approach to the time dynamics of HIV infection.

In this work we use the cellular automata model introduced by Zorzenon dos Santos and Coutinho [1] to study the statistic behavior of time dynamics of HIV infection by means of the RMT. In Section 2, we describe the cellular automata model used to study the evolution of HIV infection and we also present the time evolution of density of infected cells as generated by the model. A brief review about equal-time cross-correlation matrix and RMT is made in Section 3. Finally, in Section 4 we show our results and discussion.

2. Cellular automata model for the dynamics of HIV infection

In the cellular automata model used by Zorzenon dos Santos and Coutinho [1] the square lattice is composed by cells that can be in one of four possible states: healthy, infected-1, infected-2 and dead. In the infected-1 state, the infected cells are able to spread the infection. The state infected-2 corresponds to infected cells which have already been recognized by the immune system.

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In the initial configuration, the system is composed by healthy cells and also by a small fraction of infected cells, p_{HIV}, which are randomly distributed on the lattice. The infection process is governed by four rules:

(1) A healthy cell will become an infected-1 cell if there is at least one infected-1 cell in its neighborhood (Moore neighborhood), or if there are at least R infected-2 cells in its neighborhood;
(2) After spend τ time steps in the same state, an infected-1 cell will become an infected-2 cell, in which τ is the time necessary for the immune response;
(3) An infected-2 cell will become a dead cell in the next time step;
(4) A dead cell will become a healthy cell with probability p_{repl}. If it happens, the healthy cell will become an infected-1 cell with probability p_{infec}.

After the update of the lattice according to the rules described above one time step is counted which corresponds to one week.

In Fig. 1 we show the density of infected cells as a function of time, obtained from the model of Zorzenon dos Santos and Coutinho [1], in which the initial conditions are $p_{HIV} = 0.05$, $p_{infec} = 10^{-5}$ and $p_{repl} = 0.99$, $\tau = 4$ and $R = 4$. We have used a lattice of size equal to $L = 700$ and the results are obtained from averages over 500 distinct simulations. We can clearly notice a qualitative behavior very similar to the one presented by the dynamics of the HIV infection. In the period between 0 and 12 weeks we verify the first phase of the dynamics (primary infection), that is characterized by a peak of the infected cells. In the second phase, the clinical latency, we observe three regions which are delimited in Fig. 1: In region (a) the concentration of infected cells is very small and presents a very slow increment with time; in the second regime (b) we verify an augment of the fluctuation of the concentration of infected cells in which the curve presents a transition region with an inflection point leading to another regime (c) that is characterized by a faster increasing of the concentration of infected cells leading to the development of AIDS. In the third phase (d) we observe the onset of AIDS.

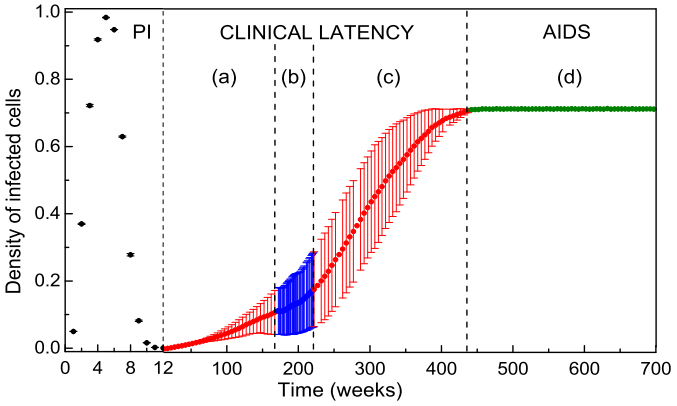

Fig. 1. Time evolution of the density of infected cells obtained from the simulations. The results are obtained from averages over 500 simulations. We used lattices with size $L = 700$, $p_{HIV} = 0.05$, $p_{infec} = 10^{-5}$, $p_{repl} = 0.99$, $\tau = 4$ and $R = 4$. PI means primary infection.

We can better understand the behavior of the system by looking at the snapshots of five distinct time steps of some realizations of the dynamics. In Fig. 2(a) we can visualize the system during the primary infection period. After the introduction of the infected cells, pulses of these cells with width $(\tau + 1)$ are generated and propagate in all directions. Around the fifth week of the infection process one can notice a peak in the concentration of infected cells and almost all the sites of the lattice are composed by cells of type infected-1 and infected-2 (which are represented in yellow and green, respectively). From this time the concentration of infected cells decreases and the end of the primary infection phase is observed when the number of time steps is equal to $2(\tau + 1)$.

After this initial phase new infected cells will be originated when dead cells are replaced by infected-1 cells. They generate structures like the ones showed in Fig. 2(b), which spread over the lattice in a much longer time that the one observed in primary infection. As long as these structures increase they can occupy the whole lattice (see Figs. 2(c) and 2(d)), incrementing the number of infected cells until they reach a stationary state. At the end of this long period in which the increase of these structures is observed, we verify another pattern in which the distinct cells are randomly distributed in the lattice with the predominance of the infected cells (Fig. 2(e)), characterizing the onset of AIDS.

3. Cross-correlation and random matrix theory

In this section, we will do a brief review about equal-time cross-correlation matrix [14] and RMT [8]. Their concepts will be applied to study the time dynamics evolution of HIV infection statistic in the next section.

The equal-time cross-correlation matrix $\mathbf{C}$ is obtained from an M-dimensional temporal series set H_{ij} with length T, where $i = 1, \ldots, M$ and $j = 1, \ldots, T$ with $M \leq T$. The correlation matrix is given by

$$\mathbf{C} = \frac{1}{T}\widetilde{\mathbf{H}}\widetilde{\mathbf{H}}^t, \tag{1}$$

where index t is a transposed of matrix and the $\widetilde{\mathbf{H}}$ matrix elements are built from temporal series set as following

$$\widetilde{H}_{ij} = \frac{H_{ij} - \langle H_i \rangle}{\sigma_{H_i}}. \tag{2}$$

The $\langle H_i \rangle$ and σ_{H_i} are the average and standard deviation of temporal series set. Furthermore, $\widetilde{H}_{ij}$ is an element of matrix $\widetilde{H}$

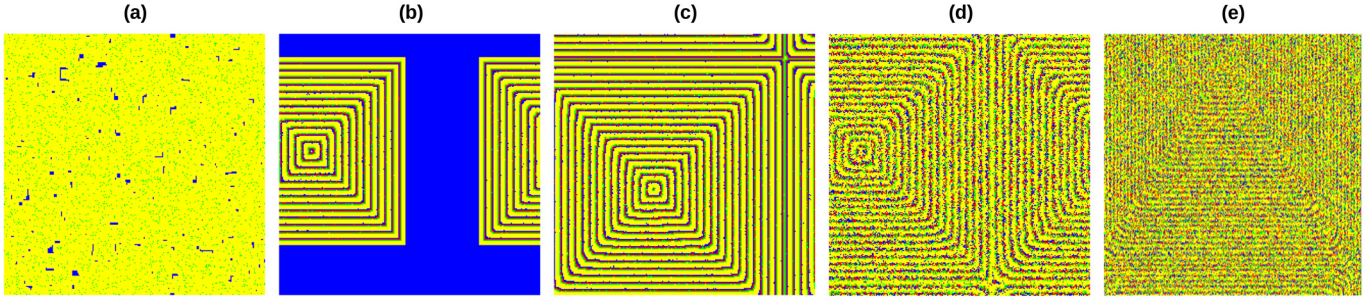

Fig. 2. Snapshots for some realizations of the dynamics at (a) primary infection period, (b) first, (c) second, (d) third region of clinical latency and (e) AIDS. In the figures, healthy cells are presented in blue, the infected-1 in yellow, the infected-2 in green and the dead cells in red. (For interpretation of the colors in this figure, the reader is referred to the web version of this article.)

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