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On cell resistance and immune response time lag in a model for the HIV infection

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Abstract

Recently, a cellular automata model has been introduced (Phys. Rev. Lett. **87** (2001) 168102) to describe the spread of the HIV infection among target cells in lymphoid tissues. The model reproduces qualitatively the entire course of the infection displaying, in particular, the two time scales that characterize its dynamics. In this work, we investigate the robustness of the model against changes in three of its parameters. Two of them are related to the resistance of the cells to get infected. The other one describes the time interval necessary to mount specific immune responses. We have observed that an increase of the cell resistance, at any stage of the infection, leads to a reduction of the latency period, i.e., of the time interval between the primary infection and the onset of AIDS. However, during the early stages of the infection, when the cell resistance increase is combined with an increase in the initial concentration of infected cells, the original behavior is recovered. Therefore we find a long and a short latency regime (eight and one year long, respectively) depending on the value of the cell resistance. We have obtained, on the other hand, that changes on the parameter that describes the immune system time lag affects the time interval during which the primary infection occurs. Using different extended versions of the model, we also discuss how the two-time scale

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dynamics is affected when we include inhomogeneities on the cells properties, as for instance, on the cell resistance or on the time interval to mount specific immune responses.

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1. Introduction

The course of the human immunodeficiency virus (HIV) infection in patients is characterized by the existence of two time scales that can be associated to clearly distinguishable stages: the primary infection, which occurs over a short time (weeks), and the latency, that takes a much longer time (years) and ends at the onset of the acquired immunodeficinecy syndrome (AIDS)[1,2]. The primary infection is characterized by a strong virus dissemination during the first weeks, which declines and almost disappears after the emergence of the specific HIV immune response [3,4]. During the following years a very low virus burden is detected. This period, called *latency period* lasts, on average, from 2 to 10 (or more) years without any drug therapy. In this stage the patient is usually asymptomatic, but there is a decrease in the number of $CD4^+$ T cells, which are the main target of the virus. When the T cell counts drop to about 30%–20% of the counts in healthy individuals, the patient is considered to have acquired the immunodeficiency syndrome. Without treatment he (or she) eventually dies from opportunistic diseases [1,2].

The first immune response that appears after contamination is the innate immune response, in which macrophages try to eliminate the virus. When the macrophage is not able to accomplish such task, it breaks the antigen and becomes an antigen presenting cell, exhibiting peptides of the virus in special receptors that may be recognized by the $CD4^+$ T cells. Once activated, these T helper cells produce chemical signals (proteins) that activate the production of B and $CD8^+$ T cells; the first of which act on the elimination of the free virus and the latter ones on the elimination of the infected cells. These specific responses are mounted on the lymphoid tissues, which provide the adequate environment where different cells and virus can interact quite strongly. According to estimates, only 2%–4% of the immune cells are circulating in blood and lymph, the rest are mostly located in the lymphoid tissue [5]. The immune cells circulate in blood and lymph during a time scale of the order of minutes and take on the order of hours to pass throughout the lymphoid tissues. This slow diffusion allows the mounting of specific responses to different infections. Therefore, lymphoid tissues play an important role on the development of the infection. However, in the case of the HIV infection, this spatial localization has a negative side, due to the fast replication and reproduction rates of the virus. Namely, the spatial localization that occurs in the lymph nodes contributes to maintain the virus in the system, since the infection can spread more easily in this environment.

In the last decades, many mathematical models have been introduced to describe the interaction between the HIV and the immune system and the development of the disease [6–9]. Most approaches used ordinary differential equations. Although many of these models succeeded to explain some aspects of the disease (e.g., changes in the cell count during the latency period or under drug treatment), none of them was able to describe the entire course of the infection, including its two characteristic time scales, for a single parameter set . One of us [10] have recently proposed a model that uses a discrete approach which can describe the entire time course of the HIV infection. This model uses a cellular automaton formalism to describe the spread of the infection in lymphoid tissues and reproduces the three-stage dynamics observed in infected patients. The model shows that, during the primary infection, each infected cell gives rise to a propagating wave of infection that eventually disappears. The permanence of the virus in the system, on the other hand, is related to the random formation of localized structures of infected cells that spread all over the tissue trapping healthy cells and eventually destroying the tissue.

In this work, we study the robustness of this cellular automaton model against variations of some of its deterministic parameters. In particular, we study whether the two time scale dynamics persist when the parameters related to the resistance of the cells and the time lag for mounting the specific immune response are varied. The increase of the cell resistance, at any stage of the infection, leads to a reduction of the latency period. Long latency periods are recovered by increasing the initial concentration of infected cells. When varying the time interval, necessary to mount the specific immune responses we observe that the two time scale behavior is preserved. We have also studied the case in which we include inhomogeneities of the cell properties. We show that the presence of inhomogeneities reduces the average latency periods.

The paper is organized as follows: in Section 2, we introduce the model and its main assumptions. In Section 3, we study the robustness of the model when two of its parameters are changed. Since there is a drastic change of behavior when one of these parameters is varied, we also study an extended version of the model in order to analyze the transition from the long latency to the short latency regimes. In Section 4 we study the role of the immune response time lag on the dynamical behavior of the original model and we also analyze the case in which the infected cells require different time lags to be detected by the immune system. We present our concluding remarks in Section 5.

2. Cellular automata model

The main contribution of the cellular automata model of [10] has been to show that the temporal pattern observed in HIV infected patients [1] may be explained by the combination of the time lag necessary to mount the usual immune response to any virus, the fast mutation and replication rates of the HIV and the spatial localization that occur in the lymph nodes. In the model the mesh structure of the lymph nodes is represented by a square lattice. This choice is based on the

assumption that the cell–virus and cell–cell interactions take place mainly in the voids of this structure when filled by a few cells. The model is then defined on a square lattice of size L^2. Each site on the lattice is occupied by a target cell which is represented by a four-state automaton that describes the possible states in which those cells may be found: healthy, infected A, infected B or dead. Healthy cells represent $CD4^+$ cells or macrophages which are the main target of the HIV. Infected A cells are those cells which have been recently infected, carry a new virus strain and have not been recognized by the immune system yet. Thus, they infect healthy cells quite easily. The model assumes that the generation of the specific immune response takes τ time steps, after which infected A cells become infected B cells, with a lower capacity of propagating the infection. At the next time step, infected B cells become dead. The state of the cells in the lattice is updated at each time step in parallel according to the rules specified below, with each time step corresponding to one week. The Moore neighborhood (8 nearest-neighbors) is adopted to define the rules. The initial configuration is mostly composed of healthy cells with a small fraction $P_{HIV} = 0.05$ of infected A cells distributed at random on the lattice. This fraction is chosen based on the findings that during the primary infection, only 1 in 10^2 or 10^3 cells harbors the viral DNA [11].

The updating rules are:

(1) A *Healthy cell* becomes infected A if it has at least either R_A infected A neighbors or R_B infected B ones. Otherwise it remains healthy.

This rule takes into account the spread of the infection that may occur due to cell to cell contact inside lymphoid tissues. In the original model, $R_A = 1$ and $R_B = 4$. In Section 3 , we focus on this rule and explore an extension of it.

(2) An *Infected A* cell spreads the infection during τ time steps and becomes infected B.

The time lag τ is the time that the immune system needs to develop a specific response to a given antigen and may vary from 1 to 8 weeks. In the original model, the authors used $\tau = 4$ for all infected A cells. This means that the time to elicit a specific immune response is always the same, since due to the high mutation and replication rates of the virus, most likely each new infected cell carries a new strain of the virus.

(3) An *Infected B* cell becomes a dead cell in the following time step.
(4) A *Dead* cell has a probability P_{repl} of being replaced by a new cell, in order to mimic the incoming of new cells due to the circulation of blood and lymph. The new cells have a probability P_{infec} of being infected A and $1 - P_{infec}$ of being healthy.

The replenishment probability P_{repl} may vary from individual to individual. However, in the original model, the authors chose $P_{repl} = 0.99$ mimicking the high ability of the immune system to replace the cells that are killed due to the infection.

The introduction of new infected cells represents either cells that come from other compartments of the immune system or the activation of quiescent infected cells. The adopted $P_{infec} = 10^{-5}$ is based on experimental findings that indicate that 1 in 10^4 or 10^5 cells in the peripheral blood expresses viral proteins [12].

As already mentioned, the model considers that each new infected cell carries a new virus strain, a rule that takes into account the high mutation rate and fast replication of the virus. Once inside the cell, the virus uses the cell machinery to replicate, a process during which errors can occur. In the case of the HIV, it is estimated that one mutation occurs per generation (on average, two generations per week) [16,17]. We might expect, then, that the immune system is being constantly stressed due to the fact that it needs to develop a new response to each new infected cell. In the original model the time necessary to mount the specific immune response to any viral strain is constant. In Section 4, we discuss the consequences of varying the value of τ.

The results obtained with the original model for the time evolution of the concentration of infected and healthy cells are in excellent agreement with the experimental data showing the observed three-stage dynamics [10]. Computing the averages and dispersions of the concentrations obtained using over 500 different initial conditions with the same set of parameters $P_{HIV} = 0.05$, $R_A = 1$ $R_B = 4$, $P_{infec} = 10^{-5}$, $P_{repl} = 0.99$ and $L = 700$, it may be observed that the primary infection displays a small dispersion while the error bars are quite large for the latency periods. Depending on the initial distribution of infected cells, the dispersion of the latency period may vary between two and ten or more years. An interesting result is that the entire course of the infection may be associated to the transient behavior between the initial configuration and the steady state. The simulations of the model also show that, while during the primary infection each infected cell gives rise to a wave of infected cells that eventually vanishes, the persistence of the virus during the latency period in the system may be associated to the formation of spatial structures of infected cells that behave like a continuous source of infected cells. Those structures grow and spread all over the lattice (at which point the system achieves its steady state), trapping the uninfected cells. The authors of [10] correlate such structures with aggregates of infected cells called syncytia which are observed in in vitro experiments and are considered in the literature as a possible cause of the virus permanence in the system [2]. In this case, the steady state of the model corresponds to the destruction of the tissue which is observed in lymph node biopsies of patients that have died from opportunistic diseases. It was later shown [14] that, due to the geometrical features of such structures, the stationary concentrations of healthy and dead cells can be approximated by $1/(\tau + 3)$ and the infected cell concentration by $(\tau + 1)/(\tau + 3)$.

Recently, Figueiredo et al. [13] have investigated the role of the neighborhood and of the dimensionality on the robustness of the model. They have shown that the results for square and triangular lattices are qualitatively similar, but that for cubic lattices the latency period becomes shorter, since the number of neighbors increases and therefore the infection propagates faster. However, a rescaling of the parameters would lead to the recovery of the long latency periods. They have also shown the

robustness of the dynamics of the model with respect to changes of some its stochastic parameters [18].

In the next sections we discuss, respectively, the role of the parameters associated to the cell resistance and to the time lag necessary to generate the specific immune response, during which each new infected cell is free to contaminate healthy cells (also see Ref. [15]).

3. Cell resistance

In the model, infected B cells cause less harm to the system than infected A ones: it is necessary to have a greater number of infected B than infected A cells in order to infect a neighboring healthy cell. Infected B cells represent cells that are already under the control of the immune system and, therefore are less harmful. It is not surprising then, that any change in the value of R_B does not affect the overall features of the evolution of the infection, as shown in Fig. 1a. In fact, if we let R_B vary from 1 to 9, we observe the same two time-scale dynamics as in the original model ($R_B = 4$). By increasing R_B from 1 to 4, the average latency period varies from 5 to 8 years. By setting $R_B = 9$, we can analyze what happens when infected B cells are completely harmless (since each cell has only 8 neighbors). Contrasting this case with the case with $R_A = R_B = 1$ the average latency period doubles from 5 to 10 years. Therefore, increasing the cell resistance to infections by cells that are about to die, R_B, reduces the probability to form target structures and increases the average latency period of the sample. For the sake of clarity, in Fig. 1(b) we show the behavior of the three cell densities (healthy, infected and dead) as a function of time for $R_B = 1$.

The parameter R_A, however, plays a much more important role on the dynamics of the infection. For instance, if we set $R_A = 2$ and keep all other parameters as in the original model, we obtain the concentrations shown in Fig. 2 and the spatial patterns of Fig. 3. $R_A = 2$ represents a situation where healthy cells need a higher concentration of infected cells in their vicinity to get infected. Contrary to what we could have expected, such increment of the healthy cells resistance does not increase the latency period. Actually, the system is less effective in controlling the infection and the latency period is considerably shorter than in the case with $R_A = 1$. Somehow, increasing the resistance of healthy cells to get infected by infected cells that are in the early stages of their infection favors the formation of aggregates of infected cells, reducing the average latency period drastically. For $R_A = 1$, each infected cell gives rise, almost simultaneously, to a single wave of infected cells that eventually collide and vanish or, very rarely, gives rise to a target structure. In the case of $R_A = 2$, only the occurrence of two infected cells in any given neighborhood gives rise to such single waves. Therefore, on average, these waves will start at a different time for each infected cell. This asynchrony of the wave initiation changes the dynamics in a way that favors the formation of targets at the very beginning of the infection (as shown in Fig. 3a). Therefore depending on the value of R_A there are two regimes: one with a long ($R_A = 1$) and one with a short ($R_A = 2$) latency period.

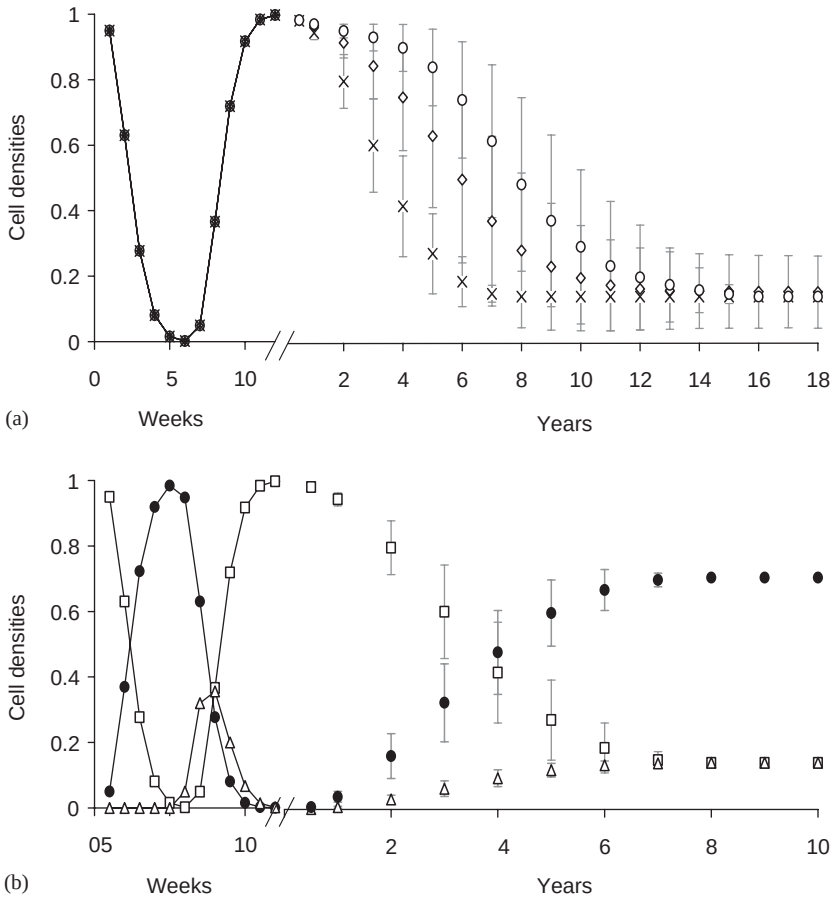

Fig. 1. (a) time evolution of healthy cell densities for $R_B = 1$ (crosses), $R_B = 4$ (open diamonds) and $R_B = 9$ (open circles) based on 50 distinct simulations. (b) density of healthy cells (open squares), infected cells (filled circles) and dead cells (open triangles) for $R_B = 1$. The other parameters used in both figures are the following: $L = 700$, $R_A = 1$, $\tau = 4$, $P_{HIV} = 0.05$, $P_{infec} = 0.00001$ and $P_{repl} = 0.99$.

Since the model is discrete in space and R_A can only take on integer values, the transition between these behaviors cannot be studied smoothly.

In order to study the transition from the $R_A = 1$ to the $R_A = 2$ regimes we decided to redefine the first rule of the original model by introducing a new parameter that allows us to tune the system into situations that are intermediate between both regimes:

1. If a *healthy cell* has exactly one infected A neighbor, it has a probability P_1 of becoming infected A and (1-P_1) of remaining healthy. A *healthy cell* becomes infected A if it has two or more infected A or at least R_B infected B neighbors. Otherwise, it stays healthy.

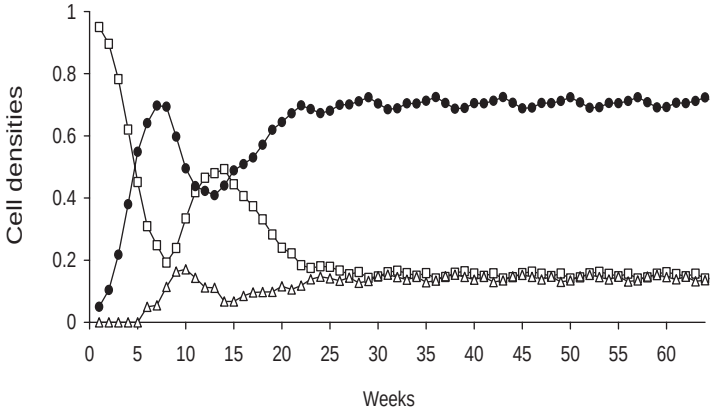

Fig. 2. Cell densities as a function of time: healthy cells (open squares), infected (A + B, filled circles) and dead cells (open triangles). Average over 50 simulations. The parameters are the same used in Fig. 1 except by the fact that $R_A = 2$ and $R_B = 4$.

The new rule is such that the case $P_1 = 0$ corresponds to $R_A = 2$ and $P_1 = 1$ to $R_A = 1$. When P_1 takes on any value between these two limiting cases, $R_A = 1$ for a fraction P_1 of the healthy cells while $R_A = 2$ for the rest (1-P_1). In Fig. 4a we show the results for the mean latency period and standard deviation when P_1 is varied between 0 and 1, averaging over 100 samples. Note that when $R_A = 2$ for most cells (small P_1), the survival rate of the patient is smaller than one year. However, increasing the fraction of $R_A = 1$ cells beyond 70% leads to a fast increase of the average latency period which achieves its maximum at $P_1 = 1$. In the inset of Fig. 4a we show the time evolution of the infected A cells for three different values of P_1. While for $P_1 = 1$ the appearance of the target structures is quite random (leading to different latency periods), an aspect which is reflected by the large error bars, in the other cases the time evolution of the system is quite similar (small error bars) due to the fact that those structures appear very early during the course of the infection (see Fig. 3).

In order to test if it would be possible to recover the three-stage dynamics with long latency periods using $R_A = 2$, we have varied the initial concentration of infected cells. By doing this, we recovered the behavior observed in the original model as shown in Fig. 4b. In contrast to what happens for $P_{HIV} = 0.05$, we reobtain long latency periods for $P_{HIV} = 0.35$ and smaller P_1. For instance, we obtain a mean latency period of 2 years in Fig. 4a only for $P_1 \geqslant 0.90$, while in Fig. 4b this is obtained for $P_1 \approx 0.60$. By increasing the amount of initial infected cells (P_{HIV}), the probability of having two infected cells in the neighborhood of a healthy cell increases, and a much larger amount of cells (compared to the case of $P_{HIV} = 0.05$) will give rise to the single wave of infected cells recovering the kind of behavior that leads to longer latency periods. The role of P_{HIV} on the dynamics of the model (with the modified rule 1) is summarized in Fig. 5.

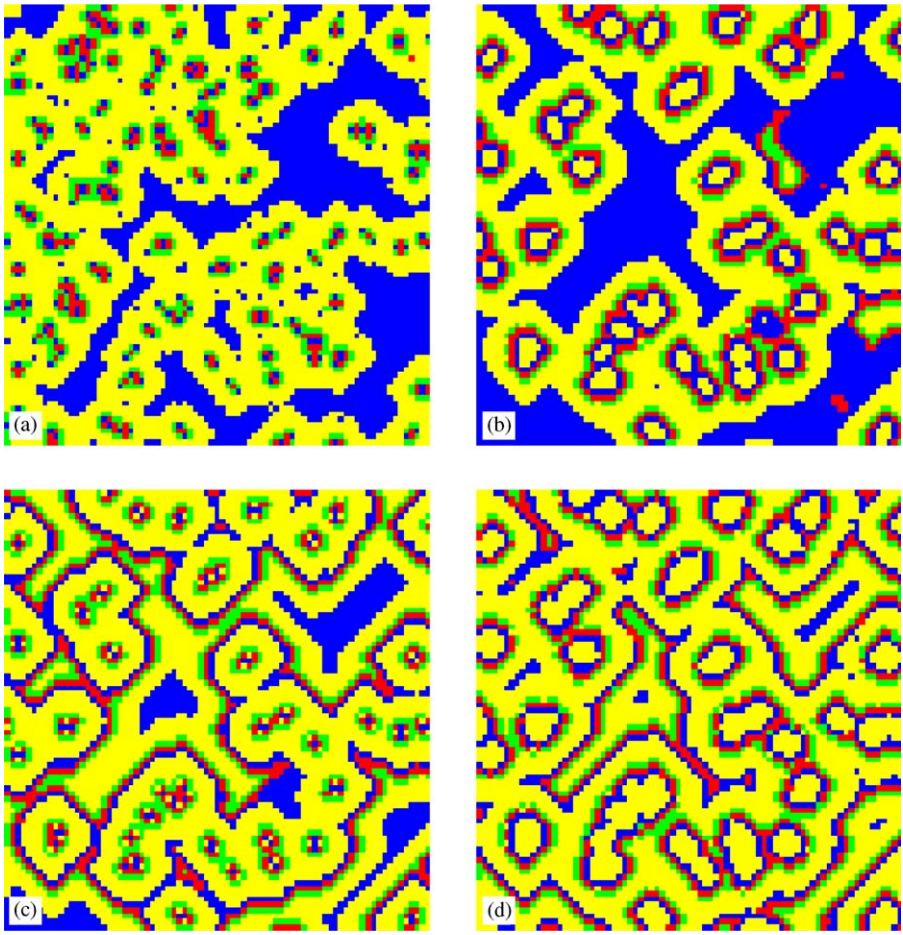

Fig. 3. Four snapshots of the spatial configuration of the lattice at different time steps, for the same parameters used in Fig. 2. From (a) to (d) they correspond, respectively, to 5, 15, 20 and 30 time steps starting from initial configuration. The color code used is: healthy cells in blue, infected A in yellow, infected B in green and dead cells in red.

4. Immune response time lag

The time lag needed to generate a specific immune response depends on the antigen, and may vary from 1 to 8 weeks [10]. In the original model, this time lag τ is held constant and equal to 4, meaning that the immune system would behave in the same way when developing the specific immune response to the new strains of the virus. Therefore, one would be tempted to ask what happens if τ is not equal to 4 but, for instance, to any integer between 1 and 6. In this section, we explore the consequences of such change by keeping the parameter fixed and by investigating the

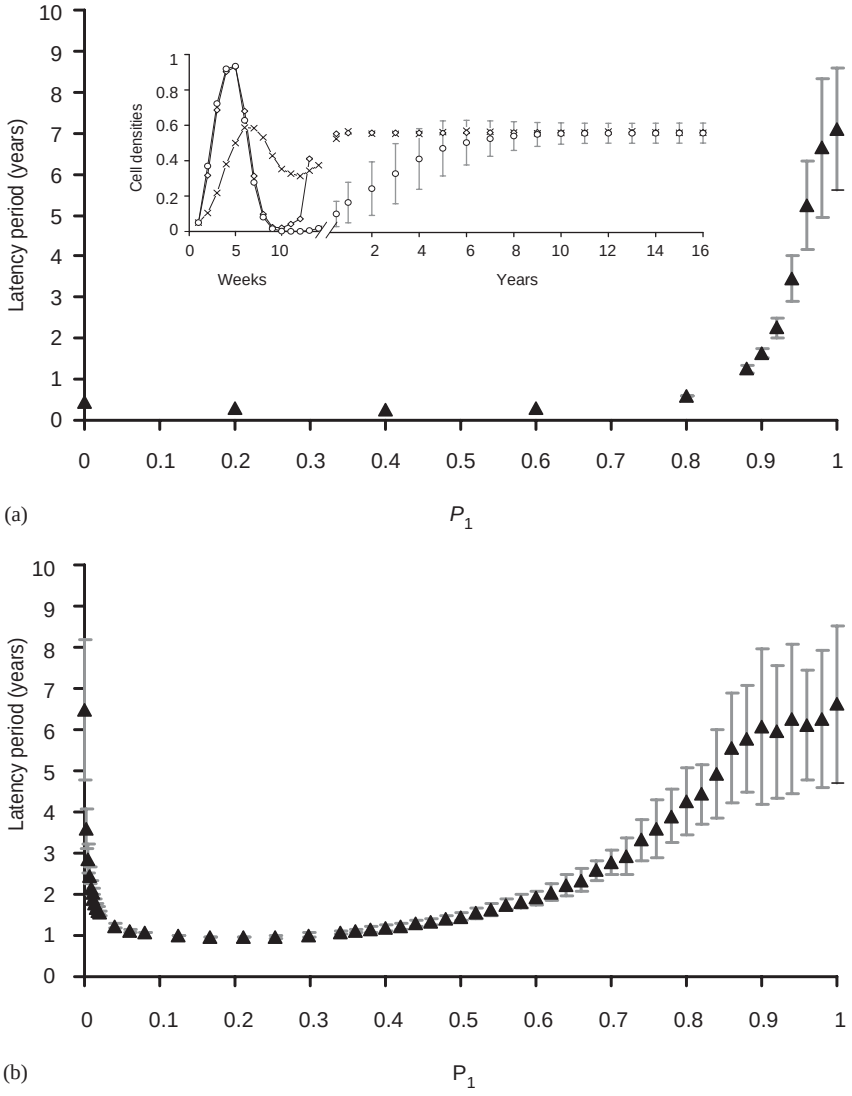

Fig. 4. (a): Latency period as a function of P_1 with $P_{HIV} = 0.05$. Each filled triangle on the plot corresponds to a mean latency period computed over 100 samples and the error bars are their standard deviation. Inset: infected A cell densities as a function of time for $P_1 = 0$ (crosses), $P_1 = 0.8$ (open diamonds) and $P_1 = 1.0$ (open circles); (b) The same as in (a) but with $P_{HIV} = 0.35$. The parameters are the same as those of the previous figures.

changes in the dynamics when considering that this time lag can vary from strain to strain.

We show in Fig. 6a the density of healthy cells and in Fig. 6b the density of infected A cells as a function of time for different fixed values of τ. Note that $\tau = 4$

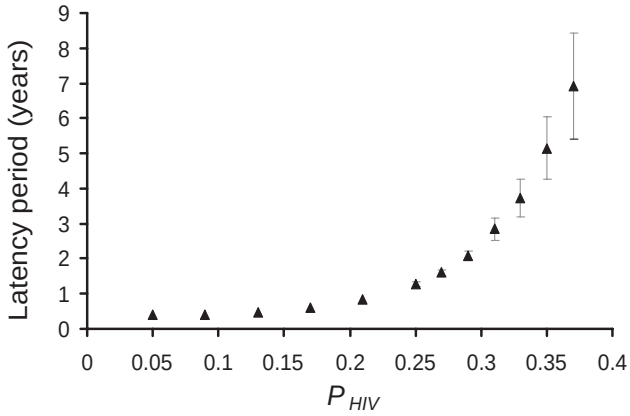

Fig. 5. Latency period as a function of P_{HIV} for $R_A = 2$. Each filled triangle represents an average latency period over 100 simulations. The other parameters are the same adopted in Fig. 2.

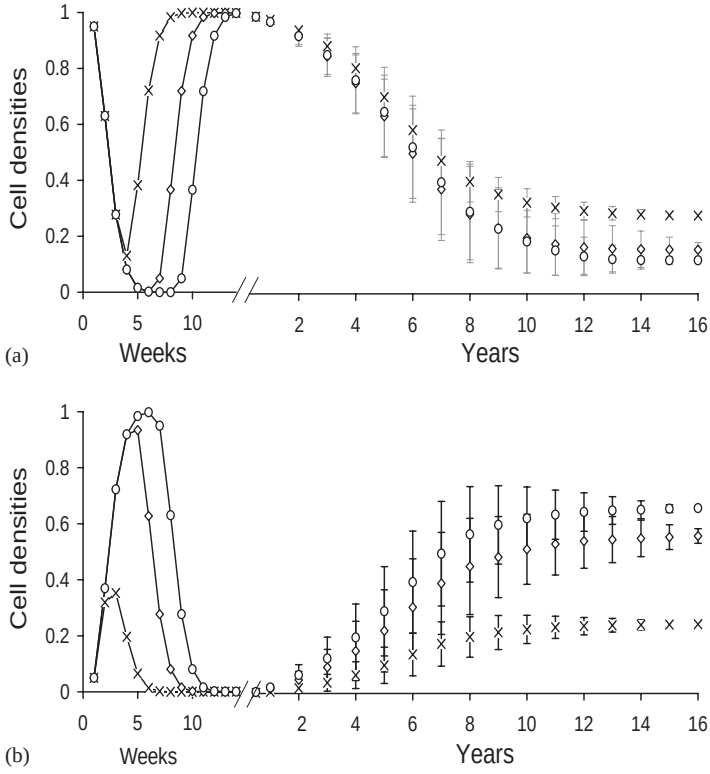

Fig. 6. Time evolution of healthy cell densities (a) and infected A cell densities (b) for $\tau = 1$ (crosses), 4 (open diamonds) and 6 (open circles) averaged over 100 simulations, keeping the other parameters as in the original work.

corresponds to the original model [10]. The behavior is qualitatively similar for all the cases shown, but both the primary infection duration and the maximum density of infected A cells during the primary infection increase with τ. When we add the densities of infected A and B cells we observe the same trend, with the maximum total density of infected cells decreasing by 30% when τ is varied from 4 to 1. This can be easily understood since it takes longer for infected cells to die and be replaced as τ is larger. Note that changes in the time lag does not affect the overall behavior of the latency periods.

In order to investigate the behavior of the model when different time lags can coexist we modified the second rule in the following way:

- The value of τ, during which an *Infected A* cell will spread the infection is assigned for each new infected cell according to a probability distribution. For the sake of simplicity and in order to study a small perturbation of the original model we define the probability distribution as follows: $P_{\tau=3} = 0.001$, $P_{\tau=4} = 0.999$, which corresponds to 1 in 1000 new cells having a different time lag.

With this extended rule we have obtained that the mean latency period is drasticaly reduced to one year as shown in Fig. 7. Note that also in this case the latency period becomes shorter because a large number of targets appear soon after the primary infection leading to the steady state very fast. This larger number of targets is again due to the asynchrony of the cells that generate the single waves.

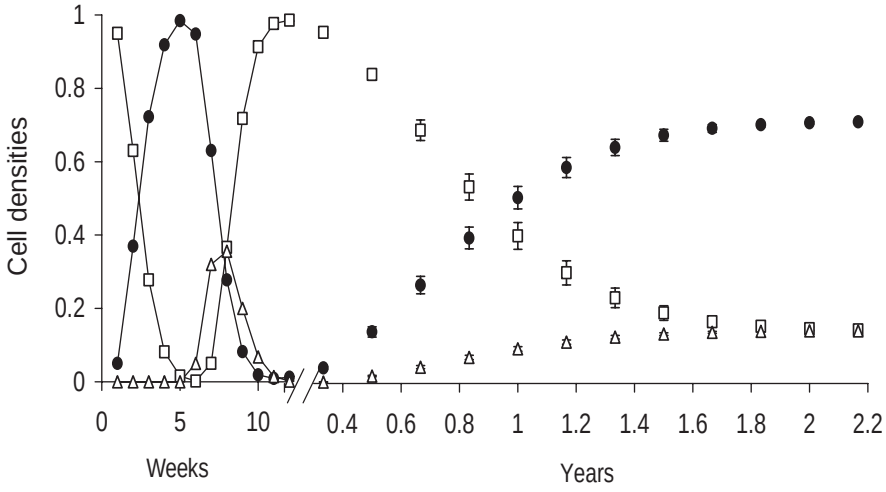

Fig. 7. Cell densities as a function of time: healthy cells (open squares), infected ($A + B$, filled circles) and dead cells (open triangles), when considering inhomogeneities on the generation of the specific immune response to different strains according to modifications introduced in the second rule. We have not changed the other parameters with respect to the previous choice.

5. Conclusions

We have investigated the robustness of the Zorzenon dos Santos and Coutinho model [10] under changes in the parameters R_A and R_B, which are associated to the intrinsic cell resistance, and τ, the immune response time lag necessary to develop the specific immune responses. These parameters are related to the deterministic rules of the model. The parameters associated to the cell resistance have different effects on the evolution of the system. For instance, changes in R_B modify the dynamics only slightly, exhibiting long latency periods. These results indicate that the B stage of infected cells is not essential to the dynamics since it works like a noise effect. Actually it increases the probability of forming the target structures that leads the system to its stationary state. On the other hand, R_A plays a more important role. As shown in Fig. 2, the latency period shortens from ~ 8 to 1 year when we turn R_A from 1 to 2, keeping all other parameters equal to those of the original model. Modifying the first rule of the automaton we could study this transition in more detail. The control parameter used was the probability P_1. We found a range of P_1 values in which there are long latency periods, in agreement with experimental findings, showing the robustness of the model. The immune response time lag τ did not show a great influence on the overall dynamics, although the primary infection gets longer if we increase τ. Nevertheless, when we modify the second rule of the automaton including the possibility of having a different time lag to generate the specific immune response to a very small number of new strains, the latency period was significantly reduced. This is due to the appearance of many targets on the lattice, which can be understood as the consequence of an asynchrony effect, as explained at the end of Section 4. From the immunological point of view, this means that developing the same kind of response to any strain of the HIV makes the system more efficient in dealing with the infection.

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