

The dynamics of the HIV infection: a time-delay differential equation approach

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Abstract.

In this work we introduce a differential equation model with time-delay that describes the three-stage dynamics and the two time scales observed in HIV infection. Assuming that the virus has high mutation and rapid reproduction rates that stress the immune system throughout the successive activation of new responses to new undetectable strains, the delay term describes the time interval necessary to mount new specific immune responses. This single term increases the number of possible solutions and changes the phase space dynamics if compared to the model without time delay. We observe very slow transits near the unstable fixed point, corresponding to a healthy state, and long time decay to the stable fixed point that corresponds to the infected state. In contrast to the results obtained for models using regular ODE, which only allow for partial descriptions of the course of the infection, our model describes the entire course of infection observed in infected patients: the primary infection, the latency period and the onset of acquired immunodeficiency syndrome (AIDS). The model also describes other scenarios, such as the very fast progression to the disease and the less common outcome in which, although the patient is exposed to HIV, he/she does not develop the disease.

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1. Introduction

After almost three decades of research attempting to understand the dynamics of HIV infection, many aspects of its underlying mechanisms remain unrevealed. Understanding the three-stages dynamics and two time scales has also challenged the scientific community over the past decades. Despite the intrinsic differences between individuals, the evolution of HIV infection follows a common pattern [1] that starts with the primary infection during the first weeks after contamination and is characterized by an extensive dissemination of the infection (large virus count), followed by a pronounced decline in the virus count caused by the development of the virus-specific immune response. Notwithstanding the decrease in the virus load, the system does not recover completely from the infection after the primary infection and very low concentrations of virus remain in the organism. This second stage, called the latency period, is asymptomatic and varies from patient to patient. The time-scale of the clinical latency period ranges from months to several years, and if untreated, is characterized by a progressive decrease in the number of HIV target cells, the $TCD4^+$ cells. The third phase corresponds to the onset of acquired immunodeficiency syndrome (AIDS) defined as the time when the T cell counts reaches the order of 20 – 30% of the concentration of the $TCD4^+$ cells in healthy individuals [2]. Without any treatment, the patient dies from opportunistic diseases.

Among the efforts to understand the dynamics of the disease, many mathematical models have been proposed to describe either specific aspects of the HIV dynamics or the overall behavior of the evolution of the infection. The attempts of the first two decades are reviewed in details in [3, 4] and references therein, but recent contributions still indicate an active interest in the theme [5–7]. To date, most of the proposed models have been based on differential equations (ODE and PDE) (see for exemple [3, 4, 8–12]), although discrete models have also been considered [13–16]. While most of the models proposed until 2001 were very successful in describing specific aspects of the dynamics or the primary infection or the latency period, none was able to describe the entire course of the infection employing the same set of parameters. The first model that described the three-stage dynamics and two time scale as observed in infected patients was a cellular automaton model put forward to describe the dissemination of infection in the target T cells located in the lymph nodes [15]. Recently, Stilianakis and Schenzle [17] proposed an ODE approach to reproduce the entire course of HIV infection. The model describes the targeted infection of $TCD4^+$ cells generating new variants of HIV that compete between themselves with a capacity of increased reproducibility within the selected variants that in turn leads to the immune system's loss of control over the infection. Using seven non-linear ODE' s and 22 parameters, the results presented by the authors reproduce the entire course of the infection on the time scale of days, corresponding to the very fast progression of the disease. The authors claim that although the results presented do not

reproduce the typical course, they were able to reproduce (not revealed in the paper) the whole spectrum of courses observed in infected patients by varying the parameters. In a further discussion, they mention that due to complications in the dynamics of the disease, the model loses its applicability to the third phase of the infection. According to the results and discussions presented throughout the paper the model seems to reproduce the three stages only for fast progressions of the disease (one time scale) and fails to reproduce the two time scales (days and years) observed in infected patients to describe the third phase.

Here we seek to describe the entire course of the HIV infection using a unique set of parameters and a non-linear differential equation approach that includes time-delayed terms. Our model follows the same assumptions as the cellular automata model introduced by Zorzenon dos Santos and Coutinho [15]: HIV's high mutation and rapid replication rates and the ability of the immune system to mount a new regular immune response to any non-identified HIV resulting from the virus proliferation process. However, since a time interval (τ) is necessary for the immune system to mount any specific response developing from the necessary signaling among the cells, the non-identified strain remaining during this time interval is able to disseminate the infection throughout the target cells. In the follow up, these newly infected cells would be able to produce new strains (through mutations) that may not be recognized by the immune system (IS) therefore, disseminating the infection during the same period of time.

The addition of this single delay term changes the dynamics of the model in the phase space, generating trajectories that depend on its non-local properties. These properties change the transit of the trajectories near the fixed points allowing for the description of the entire course of the HIV with the two time scale and three-stage dynamics. Time -delay effects are present in different (molecular, cellular or organ) mechanisms of various biological systems [18] and recently, other models with time delay terms have been introduced to describe HIV infection. However, in these models, the time delay either represents a finite incubation time before the release of new viruses by infected $TCD4^+$ cells [19, 20] or describes the delayed effects of the anti-retroviral drugs on the plasma viremia that leads to the viremia decay [7, 11, 21, 22]. Although these ODE models have time delay terms, they do not reproduce the two time scales and three-stage dynamics of the HIV infection as in the model we introduce.

2. The model

In order to facilitate the understanding of the model introduced herein, let us briefly summarize the main assumptions of the CA model [15]. The CA model describes the local interaction among target cells (T cells and macrophages) and the virus in the lymph nodes, taking into account the HIV's high mutation and rapid reproduction rates, as well as the fact that the immune system responds regularly to HIV as to any other virus. The target cells can be found in four states: healthy (**h**), infected (**A** and **B**) and dead (**d**) (or empty sites). Healthy cells are the target cells that may become

infected. Infected-A corresponds to the stage in which the infected cell disseminates the infection during τ time steps (the period of time necessary to mount the specific immune response) and infected-B corresponds to the last state of the infection in which the cells are recognized and killed in the next time step. The dynamics of the interaction among automata is defined by four rules: (1) **h** cells become infected if at least one nearest neighbor is infected- **A**. Since it is considered that each new infected- **A** that enters the system carries a new strain of virus, (2) asserts that infected -**A** cells spread the infection into its vicinity during τ time steps, and afterwards the infected-**A** cell turns to a less infective-**B** stage. Rule (3) describes the turnover of **B** cells into **d** cells (or empty sites) in the next time step. The regular blood flow in the system allows for the natural replenishment of the target cells in the lymph nodes, therefore (4) replaces **d** cells by **h** with probability p_{repl} or by infected-**A** cells with probability $p_{repl} * p_{infec}$, since we also consider that the empty sites may be occupied by infected cells coming from other lymphatic compartments. In the CA model, the fast dynamics of the primary infection corresponds to a rapid increase in the number of infected cells through the cycle **h**→**A**→**B**→**d**→**h**. The slow dynamics of the latency period is related to the formation of the spatial structures of infected cells. As shown in [15], these growing structures slowly compromise more and more cells, segregating and trapping the healthy ones and leading to a reduction in $TCD4^+$ cell counts. These structures are associated with syncytia (aggregation of infected cells) formation, observed in HIV cultures and in the lymph nodes of HIV patients.

Our model describes the time evolution of $TCD4^+$ cell density in healthy, infected and dead states using a set of ordinary differential equations. As in the CA model, we have differentiated the stages *A* and *B* in the population of infected cells, but in turn there are also two differentiated two stages in the population of healthy cells : h_1 corresponding to the healthy cells present in the tissue at the beginning of the HIV infection, and h_2 corresponding to the population of new cells that enter the system when the infection has already set in. If instead we consider only one type of healthy cells we will obtain the same qualitative results, but shorter latency periods, as discussed bellow. The sum of all the variables (populations) remains constant over time and the time delay terms would be included in the equations for infected-A and -B cells to describe the time necessary for the IS to convert any new *A* cell into a type *B* cell.

Therefore, the model is described by the following set of differential equations:

$$\begin{aligned}
 \dot{h}_1 &= -k_5 h_1(t) A^p - k_6 h_1 B^n, \\
 \dot{h}_2 &= k_3 d - k_5 h_2 A^q - k_6 h_2 B^n, \\
 \dot{A} &= -k_1 A(t - \tau) + k_4 d + k_5 (h_1 A^p + h_2 A^q) + k_6 (h_1 + h_2) B^n, \\
 \dot{B} &= k_1 A(t - \tau) - k_2 B(t), \\
 \dot{d} &= -k_3 d(t) - k_4 d(t) + k_2 B(t).
 \end{aligned} \tag{1}$$

where p and q represent the number of *A* neighbors required to convert healthy (h_1 or h_2) cells into newly infected-*A* cells; n is the number of *B* neighbors necessary to

infect healthy cells (h_1 or h_2). As in [15], we consider $p = 1$, $n = 4$ and $\tau = 4$. The h_2 population has no correspondent in the CA model but is expected to be more resistant to HIV, requiring a larger number q (when compared to p) of A neighbors to become infected. This assumption is based on the fact that once the virus is detected and the specific immune response is developed the system would respond faster to newly infected cells, therefore more infected cells would be necessary to infect a healthy one, once the infection has set in. The rate constants describe the different transitions between states. Two of them can be directly related to CA parameters: k_3 being the rate at which new A -cells are produced is related to p_{repl} mentioned above, and k_4 corresponds to the rate at which newly infected cells enter the system ($p_{repl} * p_{infec}$). The remaining rate constants, k_1 , k_2 , k_5 and k_6 describe, respectively, the transitions from states A to the B , B to d , and h_1 and h_2 to A .

As in the CA model [15], values were chosen for some rate constants and parameters based on certain biological data : (i) the replenishment ability of the system $k_3 O(1)$; (ii) a very low but finite probability (1 in 10000 cells of the peripheral blood harbor the viral DNA) that some of the newly infected cells entering the system would come from other compartments $k_4 \ll 1$; and (iii) since the responses to different virus can vary from a few days to 8 weeks, as in the CA model, we adopted $\tau = 4$.

The values of k_i are not freely chosen, but obey certain constraints that result from considering : i) the coordinates of the fixed points ($FP = (\bar{h}_1, \bar{h}_2, \bar{A}, \bar{B}, \bar{d})$) representing densities that should remain in the $[0, 1]$ interval; (ii) at the infected state the densities would respect the inequalities: $infected - A > infected - B > 0$ and $d < infected - B$; and (iii) $p_{repl} > p_{inf}$ otherwise would replace the empty sites only by infected-A cells. Therefore, $k_2 > k_1$, $k_5 > k_1$, $k_3 + k_4 > k_2$, $k_3 > k_4$.

3. Results

The system of equations (1) admits three FP solutions. Two, $FP_0 = (1, 0, 0, 0, 0)$ and $\widehat{FP}_0 = (0, 1, 0, 0, 0)$, represent the healthy states and a third that represents the infected state $FP_1 = (0, \bar{h}_2, \bar{A}, \bar{B}, \bar{d})$. To find its coordinates, it is necessary to solve the following equation for \bar{B} :

$$R\bar{B}^n + S\bar{B}^{n-1} + T \left[\frac{k_2}{k_1} \right]^{q-1} \bar{B}^q + U \left[\frac{k_2}{k_1} \right]^{q-1} \bar{B}^{q-1} + V = 0. \quad (2)$$

Equation (2) is obtained by making the left-hand sides from the equations of system (1) equal zero, as well as considering the condition of normalization. Once equation (2) has been obtained, it is then possible to describe the behavior of the infected B-cells, in which coefficients R, S, T, U and V are functions of the parameters of the model. Depending on the value of q (integer or not), (2) becomes either a polynomial or a transcendental equation. However, for integer $q \in [0, 4]$, the resulting analytical expression for \bar{B} is very complex and has no practical application to the analysis of FP_1 . Therefore, (2) is always solved by numerical methods.

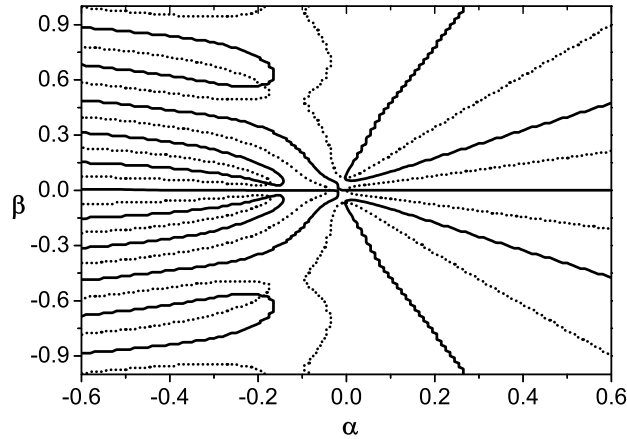


Figure 1. Location of some eigenvalues in the (α, β) plane, corresponding to the intersections of the nullclines $u(\alpha, \beta) = 0$ (solid) and $v(\alpha, \beta) = 0$ (dotted). The main features are: $u \equiv 0$ when $\beta = 0$; there are two real eigenvalues for $\alpha = 0$ (λ_0), and $\alpha < 0$ (λ_4); there is a pair of complex eigenvalues ($\lambda_{2,3}$) close to the origin; and an absence of eigenvalues with $\alpha > 0$.

FP_0 and \widehat{FP}_0 are both unstable. FP_0 is reached only for initial condition with $h_1=1$, while few heteroclinic orbits converge to \widehat{FP}_0 along the direction of its attractive manifold. To analyze the stability of the FP_1 , we follow the standard procedure using the equation for the eigenvalues of the Jacobean matrix J , $M(\lambda)=\det(J - \lambda I)=0$. For $\tau > 0$, $M(\lambda)=0$ becomes a transcendental equation since it contains terms that depend on $e^{-\lambda\tau}$. Irrespective of the value of τ , we always obtain an identically vanishing eigenvalue (λ_0), related to the conservation of the number of cells.

When $\tau=0$ there is no delay in mounting the specific immune response and its spectral equation is polynomial. For example, if we choose $k_1=0.16$, $k_2=0.2$, $k_3=0.68$, $k_4=2.5 \times 10^{-5}$, $k_5=0.6$, $k_6=0.1$, $n=4$, $p=q=1$, we obtain $FP_1=(0, 0.266, 0.361, 0.289, 0.085)$, while the spectrum is given by $(\lambda_0, \lambda_1, \lambda_{2,3}, \lambda_4)=(0, -0.705, -0.196 \pm 0.215i, -0.217)$. Since $\overline{h_1} = 0$, λ_4 describes only the decay of h_1 to 0; λ_1 indicates a fast decay to a two-dimensional space in which the slow decay towards FP_1 , actually described by $\lambda_{2,3}$, takes place. In other words, as observed in the CA model [23] the absence of time delay in mounting the specific response would favor the spread of the infection and shorten the latency period. If instead of unity we adopt $q = 1.13$, the decaying dynamics slow down as $Re(\lambda_{2,3}) = -0.169$, i. e., the effect of shortening the latency period can be reduced if we increase the resistance of the new incoming healthy cells.

For $\tau > 0$, the complex eigenvalues are obtained employing the Newton-Raphson (NR) procedure, using the notation $\lambda = \alpha + i\beta$ where $\alpha = Re(\lambda)$ and $\beta = Im(\lambda)$, $M(\lambda) = u(\alpha, \beta) + iv(\alpha, \beta)$. The eigenvalues correspond to the points where the nullclines of $u(\alpha, \beta) = 0$ and $v(\alpha, \beta) = 0$ intersect in the (α, β) plane, as illustrated in Figure 1. Graphs are very helpful for finding roots of $M(\lambda) = 0$, since they indicate the initial

values for the NR procedure. The overall picture remains essentially the same if we enlarge the region of the (α, β) plane in which the nullclines are drawn. Note that the nullclines cross each other only in the negative α region and FP_1 remains stable. The several nullcline branches, when $\alpha < 0$, indicates that both u and v oscillate and that there are an infinite number of solutions to $M(\lambda) = 0$. The influence of τ on the decay rate influences only the eigenvalues with the smallest real part, i.e., $\lambda_{2,3}$. The stability analysis shows that, when τ is increased from 0 to 4, the decay time to FP_1 is amplified by factor 7 for $q = 1.13$, and factor 5.4 for $q = 1.0$. All results of the stability analysis for $\tau = 0$ are checked by measuring the slope of the amplitude of the decaying solution to FP_1 that coincides with $Re(\lambda_{2,3})$.

If we vary the parameters respecting the conditions discussed at the beginning of this section, we note that the coordinates of FP1 change in a continuous manner and FP_1 remains a stable fixed point. Furthermore, by fixing the values of the rate constants, we find that the attracting properties of FP_1 weaken as q and τ increase. These two parameters of the model contribute to reducing the velocity at which the trajectories decay. In other words according to this model the duration of the latency period is determined by the slow dynamics on the trajectories close to the stable fixed point, which in turn is controlled by parameters q and τ . By increasing the value of q we require a larger number of infected- A cells in order to infect healthy cells h_2 , indicating that an increase in the resistance of the incoming target cells also increases the latency period. On the other hand, greater the τ , the greater the latency period or the individual's survival lifetime. Nevertheless, these features are not sufficient in themselves to account by themselves for the observed increase in the time-scale associated with the latency phase. It also depends on the presence of heteroclinic orbits generated by the time delay term, uncovered by numerically integrating the set of equations (1) using a fourth order Runge-Kutta method adapted to the time-delay approach.

As in the case of the FP analysis, a detailed investigation of all possible trajectories of the system (1) for large regions of parameter space has been carried out. For the sake of clarity, here we report only the results that illustrate the typical patterns obtained in different regions of the parameter space. Since FP_0 is unstable, almost all trajectories starting in its neighborhood are pushed away. When $\tau = 0$ the system evolves rapidly to the infected state (FP_1) and the onset of AIDS occurs a few weeks after the infection. This would correspond to cases where the disease progresses rapidly, which in general is observed in HIV patients who have been contaminated under immune-depression conditions, caused by malnutrition or other diseases that compromise $TCD4^+$ cells (e.g. tuberculosis). If we increase the value of τ from 0 to 4, the trajectory is deviated from FP_1 towards the neighborhood of \widehat{FP}_0 , where the slow transit leads to the a steady increase of latency period.

Figure 2(a) summarizes the main results obtained for this model: the appropriate description of the three-stage dynamics observed in infected individuals who have not been submitted to drug therapies. In contrast to other ODE models, here, using a unique set of parameters, we were able to reproduce the primary infection and a large

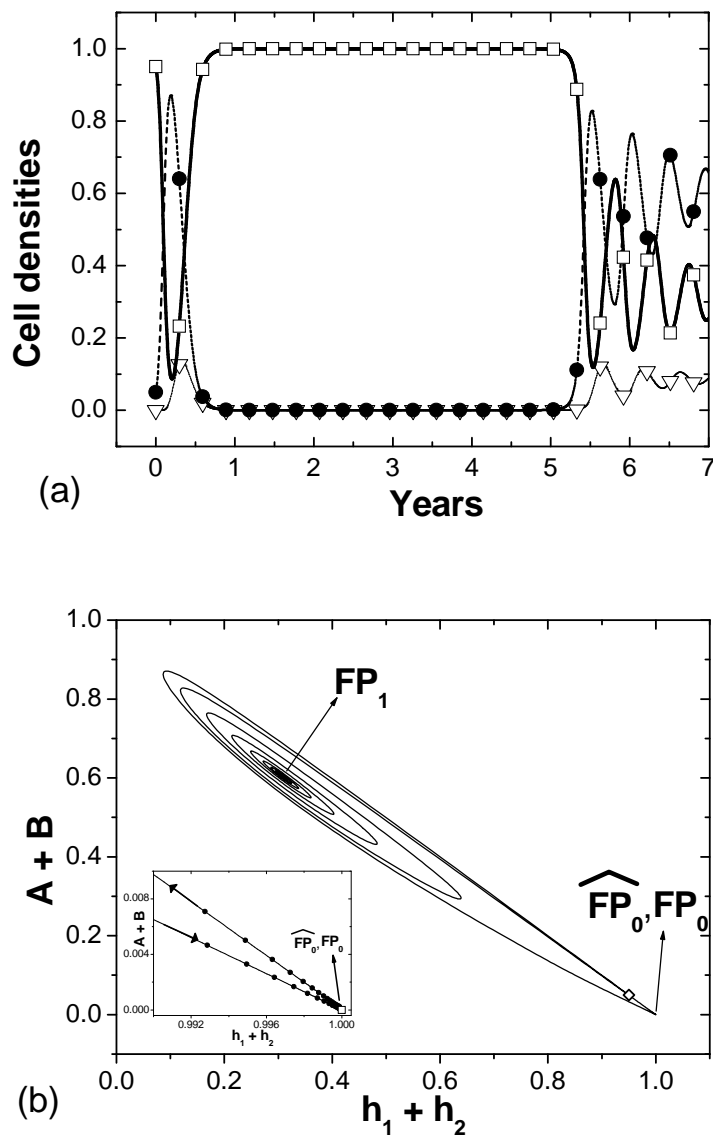


Figure 2. (a) Time evolution of HIV infection showing three distinct phases. Squares, circles and triangles represent $h_1 + h_2$, $A + B$ and d cells, respectively. The parameter values and initial conditions adopted are: $k_1=0.163$, $k_2=0.228$, $k_3=0.65$, $k_4=3.25 \times 10^{-5}$, $k_5=0.606$, $k_6=0.02$, $n=4$, $p=1$, $q=1.13$, $h_1=0.95$, $A=0.05$. (b) The same orbit in a plane projection of phase space. Diamond indicates the initial point. Inset: details of the first transit close to \widehat{FP}_0 . The trajectory first lies in the attracting manifold, but later it is pushed away from \widehat{FP}_0 along the repulsive manifold. Heteroclinic orbits occur if \widehat{FP}_0 is reached.

range of latency periods (plateau in Figure 2a) that vary from weeks to years. Moreover, a plateau is obtained on the T cell counts when the trajectory on the phase space goes towards the region of very slow dynamics, close to \widehat{FP}_0 (see Figure 2b and inset). As previously mentioned, the deviation of the trajectory in the phase space to the slow transit region largely depends on the values of q and τ . Since an increase of these parameters leads to a decrease in $Re(\lambda_{2,3})$, the return of the phase space trajectory towards FP_1 proceeds at a much slower pace, thus increasing the length of the latency period.

With regard to the estimates of the latency period, we observe that at the end of the plateau, the healthy $TCD4^+$ cell counts oscillates for some time until it stabilizes below the threshold associated to the onset of AIDS. Since the latency period is defined as the time between the end of the primary infection and the onset of AIDS, we may make a second estimate of the latency period that will be larger than that roughly estimated from the plateau. The parameter values used in Figure 2 were chosen so as to maximize the length of the latency phase. However, the same qualitative pattern, with a well-defined latency period, is observed for a finite region of the parameter space. Usually, the three-phase pattern remains stable to changes $\sim 1-2\%$ in parameter values of the reported sets. Besides this, if no distinction is made between h_1 and h_2 , ($p = q$), similar patterns are obtained, albeit with a smaller plateau. For other regions of the space parameter, the decay of the trajectory to FP_1 may proceed with less defined slow transits close to \widehat{FP}_0 and therefore lose the clearly defined latency period.

Different patterns other than those of the three-stage dynamics may be obtained for other parameter values not considered here. Without going into detailed description, a brief comment follows on the most important patterns obtained by changing the values of q and τ . For low values of q , the plateau is reduced, however, if it is increased beyond 1.18, we observe that all trajectories starting in a neighborhood of FP_0 converge to \widehat{FP}_0 . These heteroclinic trajectories, linking two unstable FPs that are not related to the infected state, describe the situation well documented in the literature, where the patient has contact with the virus but does not develop the disease. Moreover, for $q = 1.13$ and $\tau = 3$, the latency phase is still short, while, for $\tau = 5$, a sustained oscillation pattern is found due to the existence of stable limit cycles around a locally stable FP_1 . In such a case, two attracting stable sets are present. In other words for $\tau > 4.5$ the monotonic behavior disappears.

Therefore, it is possible 'grosso modo', to group the different trajectories into the following groups: i) rapid decay to FP_1 ; ii) decay to FP_1 through a latency phase, whose duration will depend on the values of q and τ ; iii) trajectories converging to \widehat{FP}_0 for q sufficiently large (>1.18); iv) stable limit cycle around FP_1 with a large amplitude, when τ is larger than 4.5

Figure 3 illustrates the average values of the cell counts resulting from the integration of (1) for $N_t = 200$ trajectories. The initial conditions were randomly chosen from the very close neighborhood of FP_0 for the same parameter values used in Figure 2. This assumption may be interpreted as if each of the 200 individuals had been

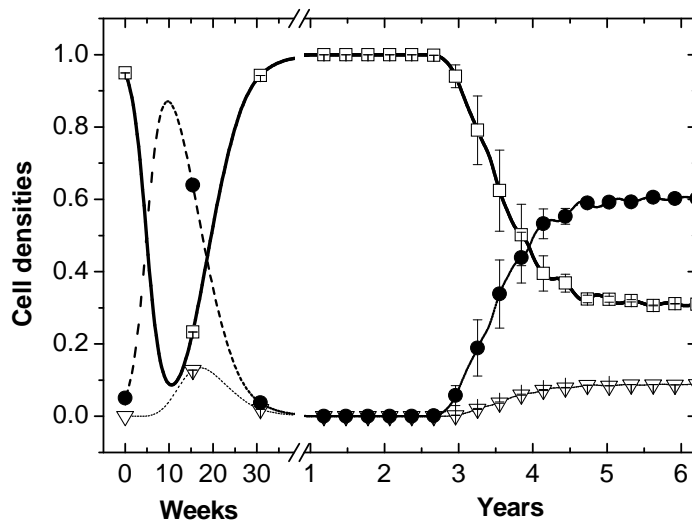


Figure 3. Average values of healthy, infected and dead cell counts resulting from 200 trajectories using different initial conditions starting in a neighborhood of FP_0 . The parameter values are the same as those used in Figure 2, as are the symbols used to describe different concentrations. The error bars indicate the standard deviation.

exposed to different initial viral loads. Similar results are obtained if slight fluctuations of the parameters are permitted to characterize different individuals of the simulated population. When we compare the results obtained to its corresponding counterparts obtained with the CA model [15], we observe the same overall dispersion pattern in both. However, in the present case the average dispersion is lower in the primary infection and after the onset of AIDS, but as obtained with the CA model it increases greatly during the latency phase. The large error bars obtained during the latency period indicate a large range of variability on the development of the disease among the 200 individuals (trajectories).

The results of this study show that a set of ordinary differential equations with time delay terms describing the retard on mounting the specific response, is able to provide a description of the entire course of the HIV infection using a single parameter set. To our knowledge, this has not been achieved previously by any other similar approach. As the model is essentially based on the rules of a CA model, our results indicate that these rules capture the main elements and mechanisms underlying the dynamics of the infection of $TCD4^+$ cells. In the CA model, spatial localization is very important for the emergence of distinct time-scales. In the model presented here, with no spatial dependence, the individual phases are found to be associated with particular structures in the phase space, which are induced by the time-delay terms. These terms describe the interplay amongst new generations of infected cells (strains) and new specific responses and increase the number of possible classes of solution. Although the number of different solutions is not as broad as those of systems with explicit spatial dependence, it is

sufficient to generate phase space structures that drive the system to regions of very slow dynamics. A more detailed discussion of all types of solution for system (1) will be published elsewhere.

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