



Modeling the three stages in HIV infection[☆]

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HIGHLIGHTS

- ▶ A mathematical model of long-term behavior of HIV infection/AIDS.
- ▶ Numerical results for two coupled feedback paths to model HIV dynamics.
- ▶ Macrophages may induce viral growth in the last stages of the infection.
- ▶ Numerical demonstration of the robustness of the model proposed.

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ABSTRACT

A typical HIV infection response consists of three stages: an initial acute infection, a long asymptomatic period and a final increase in viral load with simultaneous collapse in healthy CD4+T cell counts. The majority of existing mathematical models give a good representation of either the first two stages or the last stage of the infection. Using macrophages as a long-term active reservoir, a deterministic model is proposed to explain the three stages of the infection including the progression to AIDS. Simulation results illustrate how chronic infected macrophages can explain the progression to AIDS provoking viral explosion. Further simulation studies suggest that the proposed model retains its key properties even under moderately large parameter variations. This model provides important insights on how macrophages might play a crucial role in the long term behavior of HIV infection.

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1. Introduction

HIV targets host cells including CD4+T cells, macrophages and dendritic cells. Because of the important role of these cells in the immune system, HIV infection may induce devastating effects on a patient's health. The clinical markers of the progression of HIV infection are CD4+T cell count and plasma viral levels. In the absence of anti-retroviral treatment, the typical patient response to HIV infection has three main phases: (i) an initial acute infection; (ii) a long asymptomatic period; and (iii) a final increase in viral load with a simultaneous collapse in healthy CD4+T cell count during which AIDS appears (Fauci, 2003).

During the acute infection period (2–10 weeks) there is a sharp drop in the concentration of circulating CD4+T cells, and a large spike in the level of circulating free virus. This primary infection

period is typified by an acute syndrome with symptoms such as fever, lymphadenopathy, pharyngitis, headache and rash.

After this period, the level of circulating CD4+T cells returns to “near-normal” levels, and the viral load drops dramatically. In this asymptomatic or latent period, the patient does not exhibit any major symptoms of disease, even though HIV is continuously infecting new cells and actively replicating. Normally this latent period ranges in duration from 7 to 10 years, however, the disease progression shows great variability between individuals (Fauci, 2003).

Following this asymptomatic period, the viral load rises rapidly with a simultaneous drop in CD4+T cell count. This last stage is called AIDS, and is defined by situations where CD4+T cell counts are below 200 cells/mm³ or when certain opportunistic infections are experienced (Panel of Antiretroviral Guidelines for Adults and Adolescents, 2009).

A mathematical model may be used to help inform and analyze long term treatment options for HIV infection. However, to be useful in this context, we seek a model with several key features. Firstly, it should explain and be able to reproduce the relevant clinical data. Also, the terms within the model should have a clear mechanistic basis. Furthermore, the model should be

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appropriately robust to parameter variations that are inevitably present within the human population.

A number of previous works have examined some aspects of HIV infection, for example (Hazenberget al., 2003; Ye et al., 2004; Wang, 1997; Turville et al., 2002; Letvin and Walker, 2003; Chun et al., 1997; Cloyd et al., 2000; Kirschner et al., 1998; Grossman et al., 2002; Yates et al., 2007; Hougue et al., 2008; Ferreira et al., 2011). These and other works present a basic relation between CD4+T cells, infected CD4+T cells and viral load (Kirschner et al., 1998; Hougue et al., 2008; Nowak and May, 2000; Kirschner, 1996; Callaway and Perelson, 2002; Kirschner and Perelson, 1995; Perelson and Nelson, 1999; Xia, 2007; Tan and Wu, 1998; Dalal et al., 2008; Zorzenon dos Santos, 2001; Burkhead et al., 2009). A significant effort has been made in understanding the interaction of the immune response with HIV (Campello, 1999; Adams et al., 2004; Stan et al., 2007; Wodarz, 2001; Zurakowski and Teel, 2006). These models are able to describe either the primary infection and the asymptomatic stage of infection (Nowak and May, 2000; Kirschner, 1996; Callaway and Perelson, 2002), or the symptomatic stage (Stilianakis et al., 1997). However, none of these works describe the three stages observed in HIV infection.

One approach to mathematically model the transition from asymptomatic infection to AIDS is to introduce time-varying parameters (Bajaria et al., 2002). Of course, with appropriately selected time-varying parameters, the full course of the disease can be represented. However, in the absence of a mechanistic model of the parameter variations, it is difficult to see how such models can be used to propose new directions for therapeutic investigations.

One line of research that may help elucidate the long term mechanisms involved in HIV infection is to expand the model to include alternate viral targets alongside the commonly modeled CD4+T cells. Macrophages have been known since the 1980s to be susceptible to HIV infection. However, macrophages have received comparatively little attention in the research literature relative to the CD4+T cell host (Fauci, 2003).

To the best of our knowledge, Hadjiandreou et al. (2007) proposed the first ODE model able to represent the three stages of infection without time varying parameters during the simulation. Numerical results in Hadjiandreou et al. (2007) showed that macrophages, which can act as long-term reservoirs, might play an important role in the final stages of the infection. Nonetheless, dynamical studies of the model in Hadjiandreou et al. (2007) exhibit high sensitivity to parameter variations. These sensitivities show that for small changes of the order of 3% with respect to nominal values, the typical time course to AIDS may reduce from 10 years to 1 year or may disappear entirely. Such unusually sensitive behavior shows that the model proposed by Hadjiandreou et al. (2007) requires modification and extension to robustly reproduce the full course of HIV infection. This extension is the key contribution of this paper.

2. Mathematical model

We begin by discussing two viral reservoirs that might explain some of the very slow dynamics observed in HIV infection. A reservoir is a population of long-lived infected cells, that may permit viral replication even after many years of drug treatment. It has been suggested (see for example Chun et al., 1997; Finzi et al., 1997) that latently infected CD4+T cells could be one of the major viral reservoirs. HIV replicates well in activated CD4+T cells, and latent infection is thought to occur in resting CD4+T cells. Latently infected resting CD4+T cells provide a mechanism for life-long persistence of replication-competent forms of HIV, rendering hopes of virus eradication with current antiretroviral

regimens unrealistic. However, clinical observations (Zhang et al., 2000) reveal that the virus reappearing in the plasma of patients undergoing interruption of a successful antiviral therapy is genetically different from that harbored in latently infected CD4+T cells by HIV. These data suggest that other reservoirs may be important in the long term dynamics of HIV.

Macrophages together with Langerhans cells appear to be the first cells infected by HIV. A number of clinical studies have been conducted to explore the role of macrophages in HIV infection (Orenstein, 2001). Macrophages have been proposed to spread infection to the brain, and to form long-lived viral reservoirs (Orenstein, 2001). Based on this conjecture, Hadjiandreou et al. (2007) proposed a mathematical model which describes the complete HIV/AIDS trajectory. Simulation results for that model emphasize the importance of macrophages in HIV infection and progression to AIDS. While the model of Hadjiandreou et al. (2007) describes the whole course of HIV infection, further work is needed since the model is very sensitive to parameter variations.

We propose a simplification of Hadjiandreou et al. (2007) with the following populations: uninfected CD4+T cells (T), infected CD4+T cells (T^*), uninfected macrophages (M), infected macrophages (M^*), and the HIV population (V). The mechanisms for this model are described as follows.

Homeostatic cell proliferation. The source of new CD4+T cells and macrophages from thymus, bone marrow, and other cell sources has been assumed to be constant by many authors (Kirschner and Perelson, 1995; Perelson and Nelson, 1999)

$$\emptyset \xrightarrow{s_T} T \quad (1)$$

$$\emptyset \xrightarrow{s_M} M \quad (2)$$

s_T and s_M are the source terms and represent the generation rate of new CD4+T cells and macrophages, which were estimated as 10 cells/mm³ day and 0.15 cells/mm³ day, respectively, in Kirschner and Perelson (1995).

Moreover, HIV, as with other pathogens, triggers the proliferation of immune cells. Bilinear terms have been used to model this antigen stimulated proliferation in Hadjiandreou et al. (2007). However, it can be shown that bilinear terms give a very rapid, possibly even finite escape, final growth in the macrophage population, which does not seem to be realistic. Alternatively, if homeostatic proliferation of macrophage populations is modeled using a logistic growth, limited by viral load, this would allow convergence to a high percentage of the macrophages being infected, without allowing the total macrophage population to expand at unrealistic growth rates. Therefore, we consider antigen stimulated proliferation rates as follows:

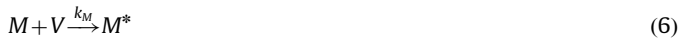
$$T + V \xrightarrow{\rho_T/(C_T+V)} T + (T+V) \quad (3)$$

$$M + V \xrightarrow{\rho_M/(C_M+V)} M + (M+V) \quad (4)$$

Proliferation parameters were adjusted to obtain the appropriate HIV trajectories with respect to clinical observations (Greenough et al., 1999; Fauci et al., 1996). The parameters obtained by trial and error are $\rho_T = 0.01 \text{ day}^{-1}$, $\rho_M = 0.003 \text{ day}^{-1}$, $C_T = 300 \text{ copies/mm}^3$ and $C_M = 220 \text{ copies/mm}^3$.

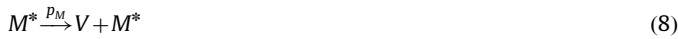
Infection process. HIV can infect a number of different cell including activated CD4+T cell, resting CD4+T cell, macrophages and dendritic cells. Dendritic cells have a pivotal role in linking cells and invading pathogens. For simplicity, we restrict attention to activated CD4+T cells and macrophages for the infection process

$$T + V \xrightarrow{k_T} T^* \quad (5)$$



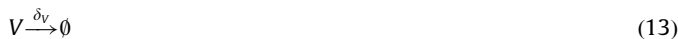
The parameter k_T is the rate at which free virus V infects CD4+T cells, this has been estimated by different authors, and the range for this parameter is from 10^{-8} to 10^{-2} mm³/day copies (Hadjandreou et al., 2007). The macrophage infection rate, k_M , is obtained by data fitting as 4.33×10^{-8} mm³/day copies.

Viral proliferation. The source of HIV, either CD4+T cells or macrophages, may be determined by the host proteins contained within their coat (Lawn et al., 2000). We model viral proliferation in infected CD4+T cells and macrophages



The amount of virus produced by infected CD4+T cells and macrophages is given by $p_T T^*$ and $p_M M^*$, respectively, where p_T and p_M are the rates of production per unit time in CD4+T cells and macrophages. The values for these parameters are in a very broad range depending of the model, cells and mechanisms. We take values from Hadjandreou et al. (2007), where p_T ranges from 0.24 to 500 copies/cell day and from 0.05 to 300 copies/cell day for p_M . Note that only a limited fraction ($\approx 0.1\%$) of circulating virions are demonstrably infectious (Chougnnet and Gessani, 2006). Some virus particles have defective proviral RNA, and therefore they are not capable of productively infecting cells. Here, as in many other mathematical models, V describes the population dynamics of free productively infectious virus particles.

Natural death. Cells and virions have a finite lifespan. This loss is represented by the following reactions:



The death rate of CD4+T cells in humans is not well characterized. This parameter has been chosen in a number of works as $\delta_T = 0.01$ day⁻¹, see for example Kirschner and Perelson (1995).

The immune system response is not included explicitly in the model, but this response is generally considered in the death rate of infected cells; which is a mixture of natural death and immune system action, in particular, the CTL response. A more detailed model would include the CTL response, however, here we ignore these details by assuming a constant death rate. This assumption is partly for reasons of simplicity. In addition, note that the immune response depends to a large extent on healthy CD4+T cells. Particularly during late stages of infection, this response is clearly significantly impaired. In addition, this faster clearance of infected CD4+T cells is also due to the direct cytotoxic/cytolytic effects of HIV replication. For these reasons, δ_{T^*} is larger than uninfected CD4+T cells. The values used for δ_{T^*} were taken from Kirschner and Perelson (1995) and Markowitz et al. (2003), and ranges from 0.26 to 1 day⁻¹.

In contrast to CD4+T cells, HIV infection is not cytopathic for macrophages and the half-life of infected macrophages may be of the order of months to years depending on the type of macrophage. These long lives could facilitate viral persistence (Brown et al., 2006). Moreover, studies of macrophages infected in vitro

with HIV showed that they may form multinucleated cells that could reach large sizes before degeneration and necrosis ensue (Orenstein, 2001). The current consensus is that the principal cellular target for HIV in the CNS (Central Nervous System) is either the macrophage or microglial cell. A large clinical study found no convincing evidence for HIV DNA in neurons (Takahashi et al., 1996). Thus macrophages and infected macrophages could last for very long periods as is suggested in Kirschner and Perelson (1995). We used δ_M and δ_{M^*} as 1×10^{-3} day⁻¹ to obtain the observed long term time course of CD4+T cells in Greenough et al. (1999) and Fauci et al. (1996).

Clearance of free virions is the most rapid process, occurring on a time scale of hours. The values of δ_V range from 2.06 to 3.81 day⁻¹ (Kirschner and Perelson, 1995; Perelson and Nelson, 1999; Xia, 2007). Notice that faster rates are widely accepted now, though for the purposes of modeling, it is sufficient to say that the kinetics of viral decay are significantly faster than other species. This gives a clear time-scale separation, and the viral loads closely track a linear combination of the productively infected cell populations, for details the interested reader is referred to Markowitz et al. (2003) and Ramratnam et al. (1999).

If we consider mechanisms (1)–(13) as the most relevant for HIV infection, then the following model may be obtained:

$$\begin{aligned} \dot{T} &= s_T + \frac{\rho_T V}{C_T + V} T - k_T TV - \delta_T T \\ \dot{T}^* &= k_T TV - \delta_{T^*} T^* \\ \dot{M} &= s_M + \frac{\rho_M V}{C_M + V} M - k_M MV - \delta_M M \\ \dot{M}^* &= k_M MV - \delta_{M^*} M^* \\ \dot{V} &= p_T T^* + p_M M^* - \delta_V V \end{aligned} \quad (14)$$

In the next section, we shall show that even given the simplicity in system (14), compared with other macrophages models (Kirschner and Perelson, 1995; Perelson and Nelson, 1999; Hadjandreou et al., 2007); we can obtain the long-term dynamics in HIV infection with a behavior that is suitably robust to parameter variations.

3. Results

For initial condition values, previous works are considered (Kirschner and Perelson, 1995; Hadjandreou et al., 2007): CD4+T cells are taken as 1000 cells/mm³ and 150 cells/mm³ for macrophages. Infected cells are initially zero and initial viral concentration as 10 copies/ml. The model outlined is implemented in MATLAB using the parameter values presented in Table 1.

Numerical results given in Fig. 1(a) show a fast drop in healthy CD4+T cells, while there is a rapid increase in viral load. Then the immune system responds to the infection, proliferating more CD4+T cells, which gives rise to the increment in CD4+T cells.

For approximately 4–5 years, an untreated patient experiences an asymptomatic phase, where CD4+T cell counts levels are over 300 cells/mm³. CD4+T cells experience a slow but constant depletion, meanwhile the virus continues infecting healthy cells and therefore a slow increase in viral load take place as can be seen in Fig. 1(b). At the end of the asymptomatic period, constitutional symptoms appear when CD4+T cell counts are below 300 cells/mm³. The last stage and the most dangerous for the patient is when the depletion in CD4+T cells crosses 200 cells/mm³, which is a key diagnostic indicator for AIDS. This last phase is usually accompanied by a rapid growth in viral load, then the severe immuno-deficiency frequently leads to fatal opportunistic diseases. Fig. 1(a) reveals how the model is able to represent the three stages in HIV infection and corresponds reasonably well to clinical data.

Macrophages together with Langerhans cells are considered one of the first points of infection, therefore infected macrophages may become long-lived viral reservoirs as is stated in Orenstein (2001). Immune system response promotes the proliferation of different cell lines, for this reason we can notice in Fig. 1(d) a logistic growth in

macrophages. The number of infected macrophages increases slowly but consistently over time, see Fig. 1(d). These results suggest that in the last stages of HIV the majority of viral replication comes from infected macrophages. This is consistent with the work of Igarashi et al. (2001), which states that during early infection the viral replication rate in macrophages is less than the replication rate in CD4+T cells.

The model proposed in Hadjiandreou et al. (2007) exhibits both exponential growth in macrophage population, and high parameter sensitivity. Both of these behaviors do not seem to be realistic. In our proposed model (14), a very rapid growth occurs if we used bilinear proliferation terms such as $\rho_M MV$ for macrophages. In this case, if the macrophage proliferation rate is faster than the infection rate of macrophages ($\rho_M > k_M$), then the macrophage population grows exponentially fast.

Notice that any function with logistic growth, for instance Michaelis–Menten or Hill function, can lead to more realistic results. Several models suggest logistic growth for cell proliferation, for example Kirschner and Perelson (1995) and Perelson and Nelson (1999). This means that the proliferation cell process is relevant to represent the adequate dynamics.

Another way to obtain realistic behavior is considering the homeostatic proliferation of macrophages population limited by $M+M^*$. This also would allow sigmoidal convergence to a high percentage of the macrophages being infected without explosion in macrophage population.

Table 1
Parameters values for the model (14).

Parameter	Units	Nominal value	Source
s_T	cells/mm ³ day	10	Kirschner and Perelson (1995)
s_M	cells/mm ³ day	0.15	Kirschner and Perelson (1995)
k_T	mm ³ /day copies	4.57×10^{-5}	Hadjiandreou et al. (2007)
k_M	mm ³ /day copies	4.33×10^{-8}	Fitted
p_T	copies/cell day	38	Hadjiandreou et al. (2007)
p_M	copies/cell day	35	Hadjiandreou et al. (2007)
δ_T	day ⁻¹	0.01	Hadjiandreou et al. (2007)
δ_{T^*}	day ⁻¹	0.4	Kirschner and Perelson (1995)
δ_M	day ⁻¹	1×10^{-3}	Fitted
δ_{M^*}	day ⁻¹	1×10^{-3}	Fitted
δ_V	day ⁻¹	2.4	Hadjiandreou et al. (2007)
ρ_T	day ⁻¹	0.01	Fitted
ρ_M	day ⁻¹	0.003	Fitted
C_T	copies/mm ³	300	Fitted
C_M	copies/mm ³	220	Fitted

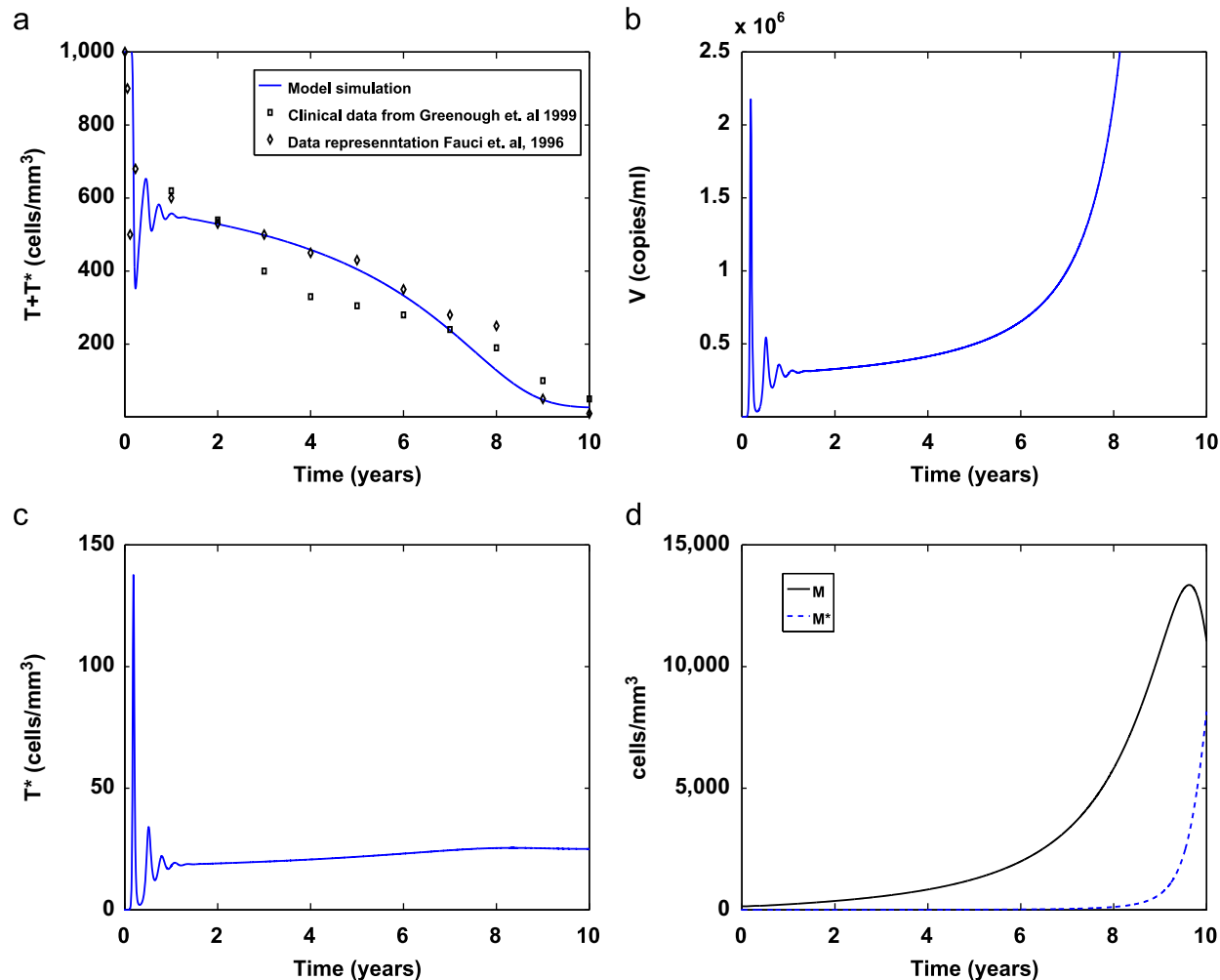


Fig. 1. CD4+ T cell, macrophage and viral dynamics over a period of 10 years. Simulation results are compared with clinical data, mean CD4+ T cell profiles of cohort subgroups taken from Greenough et al. (1999) and abstract representation data from Fauci et al. (1996) (a) CD4+ T cells, (b) virus, (c) T^* (infected CD4+ T cells), and (d) macrophages.

3.1. A possible mechanism to explain the progression to AIDS

Simulation results and parameter values help to elucidate the possible mechanisms important in HIV. The full model behavior depends on the fast and efficient infection of CD4+T cells (k_T) and critically on the slow and inefficient infection of macrophages (k_M). These factors have been tested in previous works (Kirschner and Perelson, 1995). Another important and controversial feature of our model is that we use a rate of viral production via macrophages p_M that is similar to that of infected CD4+T cells. Viral production via macrophages is typically thought to be much lower than that of CD4+T cells. For example, some studies suggest that macrophages produce a small fraction of the viral load (De Boer et al., 1997). However, Orenstein et al. (1997) reported macrophage viral production was too high to resolve by the techniques employed, indicating that viral production could be much higher than expected.

As remarked in Yates et al. (2007), CD4+T cell depletion in chronic HIV infection requires a slow process to drive the depletion of CD4+T cells. Model (14) is one possible mechanism for achieving such slow behavior.

From a control theory perspective, HIV infection can be considered as two feedback systems, see Fig. 2. One provides the fast dynamics for the early stages of infection as a result of a fast infection of CD4+T cells. The second feedback sustains a constant slow infection process in macrophages. This process has the adequate time scales of years due to both the slow infection and the long survival time conditions of macrophages.

There is a lack of information regarding infected cells in HIV. Simulation results suggest that infected macrophages may experience an increase in population as can be seen in Fig. 1(d). This is consistent with studies in rhesus macaques (Igarashi et al., 2001), using the highly pathogenic simian immunodeficiency virus/HIV type 1 (SHIV). This is an exaggerated model of HIV infection in humans that allows scientist to address certain clinical aspects of retrovirus that are difficult to study in people. Lymphoid organs such as lymph nodes and spleen for the source of the remaining virus were examined in Igarashi et al. (2001). They found that 95% of the virus-producing cells were macrophages and only 1 to 2% were CD4+T cells. Moreover, macrophages contain and continue to produce large amounts of HIV-like virus in monkeys even after the virus depletes CD4+T cells.

We can distinguish the different contributions to the viral load in Fig. 3. The viral load of infected CD4+T cells would result in

very fast convergence, showing that the final viral load explosion is not due to infected CD4+T cells; this is also known from previous works (Nowak and May, 2000; Perelson and Nelson, 1999). In this model, the final viral explosion is due to infected macrophages, nevertheless they would be unable to generate the initial peak in viral load.

Notice that macrophage population in (14) is essential for explaining the progression to AIDS. Nonetheless, other cell populations or reservoirs could also explain the dynamics. There appear to be two key factors in these dynamics: (i) the reservoir should have very long lives, and slow background proliferation and (ii) the reservoir dynamics should be largely decoupled from the CD4+T cell dynamics.

4. Model parameter analysis

While the model proposed by Hadjiandreou et al. (2007) reproduces the known long term trajectory, bifurcation analysis reveals an unusually high sensitivity to parameter variations. For instance, small relative changes (e.g. 3%) in infection rates for

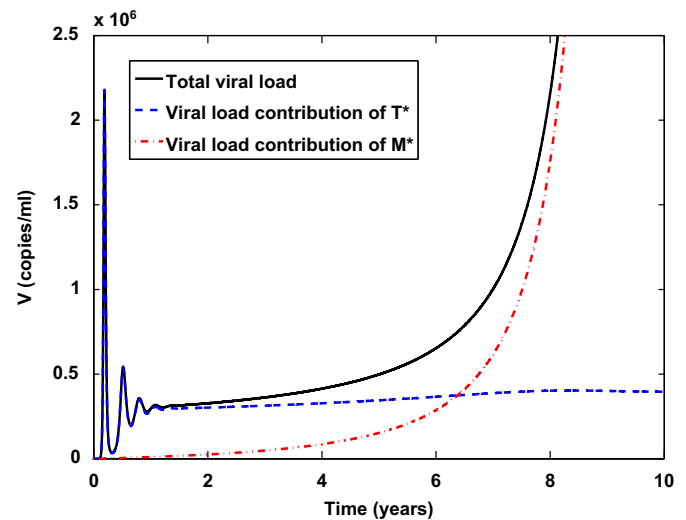


Fig. 3. Viral load contribution by infected cells.

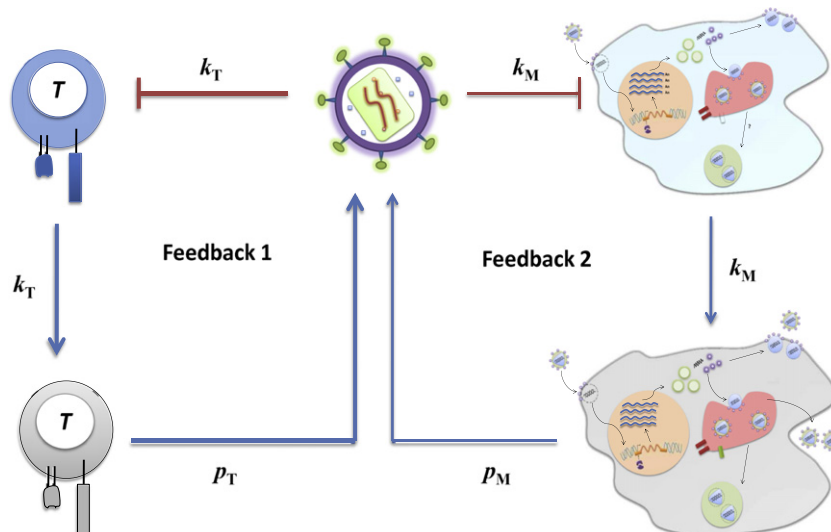


Fig. 2. HIV infection scheme.

macrophages result in different stability scenarios. These small changes in parameters can alter the simulated time to AIDS which may reduce from 10 years to 1 year or disappear entirely. Therefore, it is necessary to study the sensitivity of the proposed model to parameter variations (14).

4.1. Individual parameter analysis

In this study, we vary the parameters individually to observe the range for which model (14) shows the whole HIV infection trajectory within a reasonable time scale, given the typical range observed in clinical practice. The tested ranges in which the model provide the full behavior of HIV infection are shown in Table 2; some ranges are consistent with other works (Huang et al., 2006; Putter et al., 2002; Luo et al., 2012). We can notice in

Table 2
Single parameter variations.

Parameter	Variation
s_T	7–20
s_M	0.1–0.3
k_T	2.27×10^{-5} – 1.0×10^{-4}
k_M	1.73×10^{-8} – 1.30×10^{-6}
p_T	30.4–114
p_M	22–132
δ_T	0.001–0.017
δ_{T^*}	0.15–0.6
δ_M	1×10^{-4} – 1×10^{-2}
δ_{M^*}	1×10^{-6} – 1×10^{-2}
δ_V	0.96–2.64

Fig. 4 that the model may reproduce long term behavior despite high variations of the parameter k_T , which may range from 10% below nominal values and 220% above.

Note that higher infection of CD4+T cells speeds up the progression to AIDS. Ranges for other parameters are shown in Table 2, which reveals that parameters may be varied in a wide range while still showing the three stages of the HIV infection. With the indicated parameter variations, we observe progression to AIDS in between 3 and 15 years, in broad agreement with clinical observations. We therefore argue that (14) might be a useful model to represent the whole course of HIV infection for different patients as a result of its robustness to represent the three stages of HIV infection.

Interesting conclusions are obtained with others parameters. Consider for instance the death rate of healthy CD4+T cells δ_T : the initial intuition would suggest that increasing the death rate of CD4+T cells will hasten the progression to AIDS. Nonetheless, Fig. 4(b) shows that if the death rate of CD4+T cells is small, then the progression to AIDS is faster since CD4+T cells live for longer periods and become infected, then more virus are produced. Therefore, more infections of long term reservoirs can take place. On the other hand, if the death rate of CD4+T cells is high, then the AIDS related viral load expansion may be postponed.

Undoubtedly , CD4+T cells levels will be low with a high δ_T value, but Fig. 4(b) exposed that there may be a range of values for δ_T for which CD4+T cell count might be maintained at safe levels (> 350 cells) for many years. Clinical evidence has shown that HIV affects the life cycle of CD4+T cells (Cloyd et al., 2000). For simplicity we consider in (14) one compartment of CD4+T cells, which can be directly infected by HIV. Simulation results in Fig. 4(b) suggest that CD4+T cell infection fuels the initial peak in

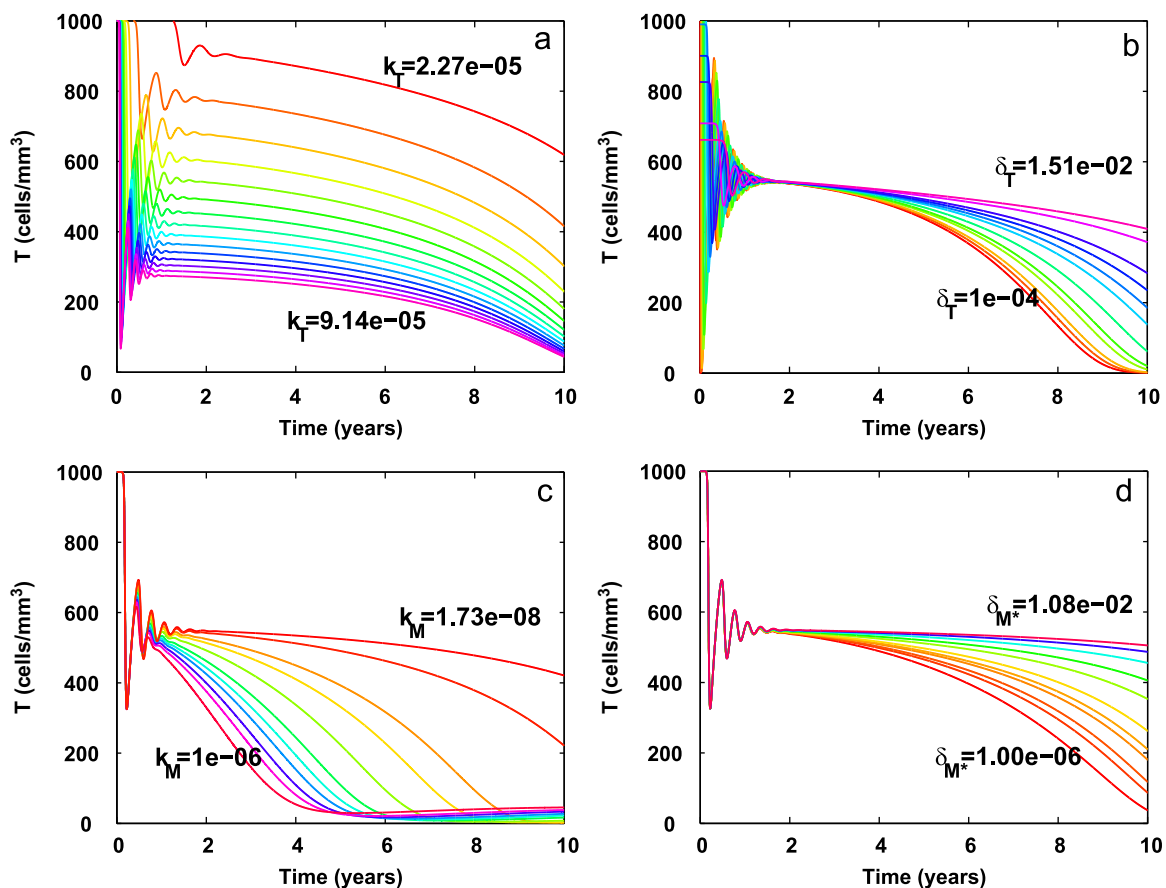


Fig. 4. Individual parameter variations of k_T , δ_T , k_M and δ_M . These figures show the CD4+T cell dynamics for parameter variations from a lower to an upper bound. (a) Variation of k_T , (b) variation of δ_T , (c) variation of k_M , and (d) variation of δ_{M^*} .

Table 3

Joint parameter variation: 1000 simulations were performed per parameter variation using a normal distribution.

Parameter variation (%)	Number of progressors	Average progression time (years)
5	1000	7.15
10	1000	7.37
30	985	7.57
50	868	7.52
80	711	6.95
100	648	6.87

viral load, which in turn infects more macrophages in the initial stage, and that sets the clock of disease progression forward.

For the case of macrophages, we tested the parameters k_M and δ_{M^*} . Fig. 4(c) exhibits how an increment in the infection rate of macrophages, will hasten the progression to AIDS. Notice that despite the wide parameter variations, the qualitative shape of the trajectory is maintained. The analysis of δ_{M^*} is important, because the long term behavior is based on the fact that infected macrophages can live for long periods, see Fig. 4(d). The life time of infected macrophages remains a subject of debate within the biological community.

We would also comment that the dynamics during the first two years of infection are largely independent of the macrophage behavior. This supports the idea that the initial trajectory is largely due to CD4+T cell dynamics and the long term behavior is based on macrophage dynamics.

4.2. Monte Carlo sampling

A Monte Carlo sampling analysis was realized to check the cross impact of the parameter variations. To this end, we perform 1000 evaluations of the proposed deterministic model (14), using different sets of parameters with normally distributed random variations about the nominal values.

Numerical study in Table 3 shows how the proposed model is able to represent the three stages of the infection even under a full set of parameter variations. For instance, nominal parameter variations of up to 10 % provide the full dynamics with slightly different time scales with an average disease progression of 7.3 years. Notice that clinicians report different time scales for progression to AIDS (3–15 years) (Greenough et al., 1999). Table 3 reveals that larger variations may be explored in the model having still a high number of progressors to AIDS. We conclude that the proposed model permits parameter perturbations of approximately 50%, while still reproducing the three stages of infection in more than 80% of the cases. Therefore, the proposed model retains its ability to describe the three stages in HIV infection even for moderately large full parameter variations.

5. Conclusions

In this paper, we proposed a mathematical model for HIV infection with an emphasis on giving a plausible explanation for the progression to AIDS. The model can represent the whole trajectory in HIV infection: primary infection, asymptomatic and symptomatic stage. Moreover, the proposed model exhibits the complete course of the infection with a robust behavior to parameter variations.

Simulation results suggest that HIV dynamics might be divided in two coupled feedback paths. One path provides the fast dynamics presented in the early stages of infection as a result of a fast infection of CD4+T cells. The second feedback path sustains

a slow but constant process of infection in macrophages. In this way, infected macrophages induce growth in the viral load in the last stages of the infection, and therefore drive the slow depletion of CD4+T cells.

In the model presented, the macrophage population is essential for explaining the progression to AIDS. Nonetheless, other classes of reservoirs could also explain this progression. The progression to AIDS in HIV infection is still an open problem for discussion in clinical circles, where further examination of macrophages may either confirm or falsify the hypothesis presented here.

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