Modelling and control of HIV dynamics

Alberto Landia, Alberto Mazzoldi, Chiara Andreoni, Matteo Bianchi, Andrea Cavallini, Marco Laurino, Leonardo Ricotti, Rodolfo Iuliano, Barbara Matteoli, Luca Ceccherini-Nelli

Department of Electrical Systems and Automation, University of Pisa, Pisa, Italy
Interdepartmental Research Center E. Piaggio, University of Pisa, Pisa, Italy
University of Pisa, Italy
Department of Experimental Pathology, Virology Section, University of Pisa, Pisa, Italy

A R T I C L E   I N F O

Article history:
Received 28 December 2006
Received in revised form
7 August 2007
Accepted 14 August 2007

Alberto Mazzoldi passed away suddenly in May 2006: this manuscript was written in memory of him.

Keywords:
Physiological models
HIV
Biomedical system
Differential equations
Numerical simulations

A B S T R A C T

Various models of HIV infection and evolution have been considered in the literature. This paper considers a variant of the Wodarz and Nowak mathematical model, adding "aggressiveness" as a new state variable in order to quantify the strength of the virus and its response to drugs. Although the model proposed is relatively simple, simulation results suggest that it may be useful in predicting the impact of the effectiveness of therapy on HIV dynamics.

© 2007 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Human immunodeficiency virus (HIV) dynamical models have been the object of intensive research in recent years. Nevertheless HIV is still not fully understood, and consequently not completely modelled. Several aspects of the pathology have been identified and modelled effectively, but other aspects, such as a more accurate model of the immune system and the therapeutic effects of drugs, are being actively researched and require more accurate experimental and theo-

retical evaluation. For example, dynamic interactions between viral infection and the immune system are particularly complex [1] and difficult to model, because they need to take into account the effects of resistance and the interactions among available drugs. Although the immune response is potentially able to attack the virus, HIV infection causes depletion of helper T-cells (CD4+), which have a primary role in the generation of the antiviral immune response. Moreover, HIV infection also attacks other immune cells, including, e.g., macrophages and follicular dendritic cells. Therefore, the acute phase of HIV
infection is characterized by an immune response that is suboptimal for the intrinsic viral activity; this reduces the capacity of the immune system and contributes to the persistence and very high mutation rate of the virus [2]. Some days after the initial burst of viral aggression, a massive increase in the number of infected cells in the lymph nodes occurs at the same time as the peak viremia. During the following 12 weeks the immune response is completed and the viremia decreases to low values, possibly below the measurement threshold [3]. After the initial phase of infection, which is characterized by a strong reduction in their number, CD4+ cells return to acceptable values. This starts a new phase of the infection, termed “clinical latency”: in the lymph nodes and spleen there is continuous replication of the virus, with destruction of immune cells [4]. In this phase, the immune system is able to control both viral and opportunistic microbial infection, so that there is no clinical evidence of the presence of the virus in the patient. After a few years a new acute phase occurs with recurrence of viremia and a decrease in CD4+ cell count. Primary viral reservoirs (sites in which infected cells are protected both from the immune system and from antiviral drugs) can lead to re-emergence of the virus upon cessation of therapy, even after many years of effective suppression [5]. Unfortunately, mathematical modelling of reservoirs is very difficult and increases model complexity [6,7].

In HIV infection, pharmacological therapy offers increased life expectancy and quality to the patient. Combined drugs are used to reduce viral replication and to delay the progression of pathology (see [8] and references therein). Highly active antiretroviral therapy (HAART) is a combination therapy that includes:

- reverse transcriptase inhibitors (RTI), to inhibit reverse transcriptase activity and prevent cell-to-cell transmission,
- protease inhibitors (PI), to inhibit the production of viral protein precursors and to prevent the production of virions by infected cells.

However, there are some limitations to the effectiveness of HAART. Infected cells have a short half-life (from days to months), but hidden reservoirs of virus contribute to an even slower disease phase [9] that makes complete eradication of the virus from the body impossible with current therapies. In addition, genetic modification of the virus and its ability to change its sensitivity to drugs complicate the problem. Therefore, several possible mathematical models have been considered to quantify the virulence of the virus and its sensitivity to the available drugs.

It is difficult to achieve a balance in a mathematical model between model complexity and a simple description of viral dynamics. Low-order models are usually too simple to be useful; conversely, high-order models are too complex for simulation purposes and have too many unknown parameters that require identification. A recent survey on the role of mathematical modelling in the optimal control of HIV-1 pathology was presented in Ref. [10]. Among all the proposed solutions, we considered the five-state dynamical model presented in Ref. [1] to be an interesting compromise between the basic third-order models and more complex models. Wodarz and Nowak include state variables that represent both the viral dynamics and the immune response in terms of the precursors of cytotoxic T-lymphocytes (CTLp), which are responsible for the development of an immune memory, and cytotoxic T-cell effectors (CTLe), which are responsible for the killing of virus-infected cells.

This work aimed primarily to improve the Wodarz and Nowak (WN) model, in an ambitious attempt to add new information to the results of simulations that would be useful to physicians in the comparison of different treatment regimens, such as when deciding when to start or switch therapy. The main equations of the model are analyzed and discussed for various categories of HIV patient (long-term non-progressors, treated and untreated fast progressors). With respect to the WN model, a new variable, denoted “aggressiveness,” is considered for the best evaluation of therapeutic protocols, instead of the free virus concentration. In order to obtain simulation results coherent with the medical findings, a close cooperation with clinical researchers, expert in HIV therapies, was helpful in testing the model.

2. Models of Wodarz and Nowak

In the literature, the basic model presented [11] for mathematical modelling of HIV considers only three state variables (expressed as cell counts in blood per cubic millimeter) inside a whole body model. The model is mathematically described by:

\[ \begin{align*}
\dot{x} &= \lambda - dx - beta uy \\
\dot{y} &= beta uy - ay \\
\dot{v} &= ky - uv
\end{align*} \]

(1)

The first equation represents the dynamics of the concentration of healthy CD4+ cells (x); \( \lambda \) represents the rate (assumed constant) at which new CD4+ T-cells are generated. The death rate of healthy cells is \( d \). In the case of active HIV infection the concentration of healthy cells decreases proportionally to the product \( beta uy \), where \( beta \) represents a coefficient that depends on various factors, including the velocity of penetration of virus into cells and the frequency of encounters between uninfected cells and free virus.

The second equation describes the dynamics of the concentration of infected CD4+ cells (y); \( beta \) is the rate of infection; \( a \) is the death rate of infected cells.

The third equation describes the concentration of free virions (v), which are produced by the infected cells at a rate \( k \), and \( u \) is the death rate of the virions.

The therapy is modelled under the assumption that RTI inhibit the infection of cells, which remain healthy. If the drug efficacy is maximal and equal to 100%, and if the system is at equilibrium before drug treatment, \( beta \) is set to zero in the model. If the drug efficacy is low, \( beta \) is substituted by \( beta' = s \beta \), with \( s < 1 \).

PI require different modelling because they reduce infection of new cells, but do not block production of viruses from cells already infected; in Ref. [12] model (1) is changed accordingly, and the effect of PI is lumped into the parameter \( k \) of the third equation.
A five-state model was presented in Ref. [1] by Wodarz and Nowak. Although maintaining a simple structure, the model offers important theoretical insights into immune control of the virus based on treatment strategies, which can be viewed as a fast subsystem of the dynamics of HIV infection. It is mathematically described by:

\[
\begin{align*}
\dot{x} &= \lambda - dx - bxu \\
\dot{y} &= bxy - ay - pyz \\
\dot{u} &= ky - uv \\
\dot{w} &= cxwy - cqyw - bw \\
\dot{z} &= cqyw - hw
\end{align*}
\]  \tag{2}

Two differential equations are added to (1) to describe the dynamics of cytotoxic T-lymphocyte precursors CTL_p(w), which are responsible for the development of immune memory, and cytotoxic T-lymphocyte effectors CTL_m(x), which are responsible for the killing of virus-infected cells. This model can discriminate the trend of infection as a function of the rate of viral replication: if the rate is high a successful immune memory cannot establish; conversely, if the replication rate is slow, the CTL-mediated immune memory helps the patient to successfully fight the infection. A detailed description of this model and of its ability to represent the dynamics of HIV infection and therapy can be found both in the original papers [1,11] and in Ref. [3], where a modified version of (2) allows investigation of a model predictive control (MPC) based treatment scheduling technique.

3. Variant of the Wodarz and Nowak model

The model developed in our research is a variant of WM model (2), which was developed in order to reach the first objective of mirroring the natural evolution of HIV infection, as qualitatively described in several clinical studies. A generalized graph of the relationship between number of HIV copies (viral load) and CD4 count over the average course of untreated HIV infection is presented in Fig. 1.

The viral dynamics shown in Fig. 1 represent a standard reference curve for a first validation of the mathematical model in the case of untreated infection; this validation has a purely qualitative nature, remembering that the disease course may vary considerably between individuals.

The second objective of the study is an attempt to introduce the impact of therapy effectiveness into HIV dynamics in a simple way, suitable for use in feedback control.

The proposed model is:

\[
\begin{align*}
\dot{x} &= \lambda - dx - rxy \\
\dot{y} &= rxy - ay - pyz \\
\dot{u} &= cxwy - cqwy - bw \\
\dot{w} &= cqwy - hw \\
\dot{z} &= cqwy - hw
\end{align*}
\]  \tag{3}

It differs from (2) in the introduction of the new state variable \( r \), the intrinsic virulence of the virus; in such a hypothesis the constant \( \beta \) of (2) is substituted with the state variable \( r \), an index of the aggressiveness of the virus. The aggressiveness of the virus can be related to the ex vivo fitness, a biological value that measures the efficiency of HIV replication ex vivo (independently of immune system control) [13]. The new equation describing the \( r \)-state dynamics increases linearly in the case of an untreated HIV-infected individual, with a growth rate that depends on the constant \( r_0 \) (a higher \( r_0 \) value indicates a higher virulence growth rate). In the model presented here, the increase of virulence is assumed to be linear: this hypothesis is consistent with the simulation results obtained in the case of long-term non-progressors patients. By extension, because the effects of HAART therapy shift the immune system to a state resembling that of long-term non-progressors, a linear increase in virulence could be an appropriate choice for modelling. Coefficients \( \mu_T \) and \( \mu_P \) represent the drug efficacy weights for specific external inputs \( f_T \) and \( f_P \), which represent RTI and PI drug delivery.

The general structure of aggressiveness (last equation of (3)) can be modified in the case of multiple drug delivery to give:

\[
\dot{r} = r_0 - \sum_i \mu_i f_i \tag{4}
\]

where \( \mu_i \) represents the drug efficacy coefficient for a specific drug \( f_i \), based on any subtype of RTI (nucleoside analogue or non-nucleoside analogue RTI).

A different model of aggressiveness may be used to consider the case of exponential dynamics: the last equation of model (3) could be modified to give:

\[
\dot{r} = (1 - \mu_T f_T)r \tag{5}
\]

In the latter case the same therapy is less efficient against a more ‘aggressive’ virus and drug efficiency should increase to counteract the increased viral virulence. Work is in progress to determine whether testing if an exponential law for aggres-
sleness could be used to model new more virulent genetic subtypes of HIV.

Combinations of antiretroviral drugs often include PI, which have different mechanisms of action from RTI. PI reduces the rate of virus production, and this action is modelled by modifying the rate $k$ of production of infected cells in the dynamical Eq. (3) to mimic the viral load.

The modified differential equation is:

$$\dot{v} = k(1 - \mu_P f P) y - uv$$

where the term $\mu_P f P$ reduces the rate $k$ of virion production depending on the efficacy $\mu_P$ of the PI drug $f P$. Note that, under the hypotheses of a constant coefficient $k$ (untreated patient), (6) is redundant if $k \gg u$, because the time response of viremia ($v$) is almost proportional to the concentration of infected CD4+ cells ($y$).

4. Results of simulation tests

Parameters of the model and their values are summarised in Table 1.

Most of the parameters were set according to earlier published estimates [14]. The remaining parameters were chosen to be consistent with biological plausibility.

The parameters $b$ and $h$, which represent the death rates of CTLp and CTLe, respectively, may be set to two different values. In the following simulations we considered the two extreme cases: the lower values correspond to the model dynamics of long-term non-progressive (LTNP) patients; the higher values model the dynamics of fast progressor patients (FP). The different values of $f_T$ and $f_P$ are set to binary values 1 (in the case of treated patients), or 0 (untreated patients). The coefficients $\mu_T$ and $\mu_P$ are used to weight the different average drug efficacies [15]. In the following simulations the cases of strong and of weak therapy are presented. Strong therapy combines the effects of the drugs such that RTI are 90% and PI are 80% effective; weak therapy corresponds to RTI at 50% and PI at 40% effectiveness.

Initial conditions, at time $t=0$, were: $x(0)=10^3$ cells $\mu l^{-1}$, $v(0)=10^4$ copies ml$^{-1}$, $y(0)=0$ cells $\mu l^{-1}$, $w(0)=10^{-3}$ cells ml$^{-1}$, $z(0)=10^{-7}$ cells $\mu l^{-1}$, and $r(0)=4 \times 10^{-7}$ ml copies$^{-1}$ day$^{-1}$.

The initial conditions of $v(0)$ can be extremely variable, because they depend on the initial infection burst (e.g., in critical cases of infected transfusions, or organ transplant).

The initial value of $r(t)$ corresponds to the published estimate [14] of the constant value of the coefficient $\beta$ of (1). The remaining initial conditions are typical values for healthy people. All simulations were implemented using the Simulink environment of Matlab$^\text{TM}$, and the numerical solutions of the differential equations employed a fixed-step continuous solver (ODE5) with Dormand Prince formula.

The simulation results are based on the following hypotheses:

- the initial burst of the viral infection is simulated with the initial condition of viral load;
- the existence of additional reservoirs of CD4+ cells was not considered, as in most of the results presented in the literature and based on the WM models.

In the following figures, the dynamics of the viral load are represented by a more informative logarithmic scale, to put into evidence both the peaks and the latency period of the viral load.

For the purposes of qualitative model validation and comparisons with the experimental results presented in Fig. 1, the relationship between viral load and CD4 cells is shown in Fig. 2. The simulation results include the clinical latency asymptomatic stage, and do not take into account opportunistic diseases. The opportunistic disease course may vary considerably between individuals and cannot be unequivocally simulated. The simulation results are seen to be consistent with the reference trends of Fig. 1.

Fig. 3 includes four subplots that show a comparison between untreated HIV-infected individuals in the case of LTNP (solid lines) and FP (dashed lines) patients. Comparison is limited to the first 3 years after the burst of infection, because a longer interval has little relevance for FP patients. The oscillations visible in Fig. 3 are consistent with the observation that,
for LTNP patients, strong immune responses in CTLe and in CTLp generate an initial rebound effect in the number of CD4 cells.

The simulation results mirror the natural history of HIV infection in the following respects:

1. The results show the presence of a correlation between the viral load (Fig. 3b) and the decline in the count of helper lymphocytes (Fig. 3a), as demonstrated in clinical studies [16, 17]. The CD4+ T-cells show a rebound typical of the acute phase of infection, followed by a constant quasi-homeostatic condition in the latency period. After the latent period, the viral burst leads to almost total cell depletion during the last phase of the infection for FP.

2. The results show (Fig. 3b) typical dynamics of HIV primary infection with a peak and a nadir of viral load and a nadir of the count of helper lymphocytes. Moreover, differences between peak and nadir values of viral load are consis-

---

Fig. 3 – Dynamic behaviour of the state variables $x$, $v$, $w$ and $z$ vs. time in the case of untreated LTNP (solid line) and FP (dashed line) HIV-infected patients.

Fig. 4 – Dynamic behaviour of the state variables $x$, $v$ and $z$ vs. time in the case of treated FP infected patients. Strong therapy (solid line) and weak therapy (dashed line), initiated 2 months after infection.
Fig. 5 – Dynamic behaviour of the state variables $x$, $v$ and $z$ vs. time in the case of treated FP infected patients. Strong therapy (solid line) and weak therapy (dashed line), initiated 12 months after infection.

- Viral loads (Figs. 4 and 5b) show a significant decrease consistent with clinical data [21].
- Interestingly, a decrease in $\text{CTL}_{\text{e}}$ (Figs. 4 and 5c) occurs in response to therapy; the extent of the decrease is directly correlated with the increase in treatment effectiveness. Experimental findings have shown a similar tendency after an initial survey of $\text{CTL}_{\text{e}}$ in patients undergoing HAART therapy [22,23].

In agreement with clinical studies [24], our results show that, in the presence of a high viral load, a delay in the institution of therapy reduces its effectiveness (compare the final values of viral load and count of $\text{CD4}^+$ cells in Figs. 4 and 5).

5. Concluding remarks

The inclusion of virulence as a new state variable in earlier WN models represents the main outcome of the study; it should be emphasised that this simple extension to WN models allows us to mirror the natural history of HIV infection and to check the effectiveness of therapy in terms of the dynamics of the state variables. An advantage of the proposed model is its direct and simple extension to earlier WN models, by using the variables $f_T$ and $f_P$ to represent the external inputs (drugs) weighted by coefficients $\mu_T$ and $\mu_P$ (drug efficacy). However, it shows intrinsic limitations due to the simple structure of all WN-based models in comparison to more comprehensive models presented, for example, in Ref. [8], where additional effects due to the impact of HIV mutations on the immune system are included, according to a stochastic process. Nevertheless, as with all earlier WN models, the proposed extension leads to simulation results in good agreement with typical
clinical findings of HIV infection, in terms both of steady-state behaviour and of transient responses.

Therefore, this extended model represents a promising candidate for testing the effects of therapy in a simple and direct way, especially in a complex case such as HAART, where the therapy needs to be optimized for reducing side effects, toxicity and resistance to medication.

Although we are aware that the possible adaptation of the parameters of the model to single patients is an extremely optimistic goal, we believe that the introduction of a control loop for testing the effects of the therapy, e.g., using a model predictive control, as proposed in Ref. [3], is difficult but attainable. Work is in progress in cooperation with clinical researchers. The use of data sets from treated patients will help us in setting the parameters of the model more precisely alongside consideration of structural identifiability issues. A final and ambitious goal is to combine real data and simulation results to classify patients into different clusters, characterized by similar responses to different therapeutic protocols.

Conflict of interest

The authors have declared that no conflict of interest exists.

REFERENCES