# MODELLING AND CONTROL OF HIV DYNAMICS

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Abstract: Various models have been considered in literature for modelling HIV infection and evolution. This paper considers a modification of the Wodarz and Nowak model, in order to obtain a simple, but effective mathematical model useful to predict the effects of a therapeutic drug regimen. After presenting several simulations for illustrating the effectiveness of the considered model, an accurate analysis of the results and some new ideas for future studies are discussed. 

Keywords: Physiological models, HIV, Biomedical system, Differential equations, Numerical simulations.

## 1. INTRODUCTION

Over the last years HIV dynamical models have been the objects of an intensive research. Nevertheless "Human Immunodeficiency Virus," (HIV) still continues to be not completely modelled. Several aspects of the pathology have been identified and modelled in an effective way, but unfortunately other aspects (especially correlated to therapeutic effects) are under research activity and require more accurate experimental and theoretical evaluations. Dynamic interactions between viral infection and immune system are particularly complex (Wodarz and Nowak, 2000). Although the immune responsiveness is potentially able to attack the virus, HIV infection causes the depletion of the cell Helper T $CD4^+$, which has a primary role in the generation of immune response. Moreover, HIV infection attacks other immune cells, as macrophages, dendrites cell, etc. Therefore, in the initial acute phase of this pathology, there is an immune response, which is sub-optimal for the intrinsic viral activity reducing ability of the immune systems. This peculiar viral activity contributes to the permanence of the virus and to its very high mutation rate (Vergu, Mallet and Golmard, 2005). Some days after the burst of the viral aggression, there is a high increase of number of virus cells at lymph-nodes, with a peak of viremia. In the following 12 weeks the immune response is completed and the viremia decreases up to low values, which can be also below the measurement threshold (Zurakowski, and Teel, 2006). After the initial phase characterized by a strong reduction, also $CD4^+$ cells come back to acceptable values. It starts a new phase of the infection, with a "clinical latency": in the lymph-nodes and spleen there is a continuous replication of the virus, with destruction of immune cells. In this phase, the immune system is apparently able to control the situation and to oppose its action of virus and of other opportunistic microbes, such that there is no particular evidence of the presence of the virus in the patients. Only after few years, a new acute phase bursts, with re-increasing of viremia and $CD4^+$ decreasing. Primarily viral reservoirs (in which

virus cells are conserved without possibility to be destruct by immune system or by external drugs) cause re-emergence of the virus upon cessation of therapy, even after many years of suppression (D. Finzi et al, 1999). Modelling of reservoirs (Ortega and Landrove, 2000), (Di Mascio et al, 2004), at the moment is one of the more difficult aspects to be implemented in the mathematical models. In this context, the pharmacology therapy offers several interesting results to an increasing of the quality and of expectation of life for the patient. Two main classes of drugs are used to reduce the replication of the virus and to delay the progression of the pathology (see Adams et al. and references therein, 2005). The so-called highly active anti-retroviral therapy (HAART), is a combination therapy including

- reverse transcriptase inhibitors, to stop the process of inverse transcription and to avoid to permit to the virus to infect other cells,
- protease inhibitors, to stop the production of precursors of viral proteins avoid the assembling the productions of virions by infected cells.

Some plain comments on the HAART can be introduced: infected cells have a half-life short (from less than one month to 6 month), but hidden reservoirs of virus contribute to an even slower disease phase (Brandt and Chen, 2001). These long lasting time phases of infection make complete eradication of the virus from the body impossible with current therapies. In addition, genetic modifications of the virus and its ability to change its response to drugs com-plicate the problem. Therefore possible mathematical model have to consider and quantify the 'force' of the virus and its response to the drugs.

In this context a mathematical model able to balance the model complexity with a simple description of the viral dynamics is a difficult task to satisfy: low order models are usually too simple to be useful, on the other hand high order models are too complex for simulation purposes and have too many unknown parameters to be identified. Some interesting models have been proposed by Wodarz and Nowak (2000), they include state variables representing both the viral dynamics and the immune responses, in terms of precursors of cytotoxic T-lymphocytes (CTLp), responsible of the development of an immune memory, and effectors of cytotoxic T-lymphocytes (CTLe).

This paper has the primary goal to improve the Wodarz and Novak model, in the ambitious attempt to add new information to the results of simulation useful to physicians for comparing different treatment policies such as when to start or to switch therapy. More in detail the main equations of the model are analyzed and discussed in various cases (healthy patients, HIV patients without and with drug treatments, evaluated on short and long times). With respect to other models, a new variable, denoted as "aggressiveness," is considered for a best evaluation of therapeutic protocols. In order to obtain simulation results coherent with the medical practice, a strict cooperation with clinical researchers expert in HIV therapies was successfully considered.

## 2. MODELS OF WODARZ AND NOWAK

The first model presented [9] considers three state variables (expressed as cell counts in blood per cubic millimetre) inside a whole body model. The model is mathematically described by:

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv \\ \dot{y} = \beta xv - ay \\ \dot{v} = ky - uv \end{cases} \quad (1)$$

The first equation represents the dynamics of the concentration of healthy $CD4^+$ cells (x); λ represents the rate (supposed constant) at which new $CD4^+$ T-cells are generated. The death rate of healthy cells is d. In case of active HIV infection the concentration of healthy cells decreases proportionally to the product βxv, where β represents a coefficient depending to various factors, as the velocity of penetration of virus into the cells, frequency of encounters between uninfected cells free virus, etc.

The second equation describes the dynamics of the concentration of infected $CD4^+$ cells (y); β is the rate of infection, a is the death rate of infected cells.

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

The therapy is considered with the following policy: reverse transcriptase inhibitors stop the infection in cells still healthy. If the drug efficacy is maximum and equal to 100%, and if the system is at equilibrium before the drug treatment, β is set to zero in the model. If the drug efficacy is imperfect, β is substituted by $\beta^* = s\,\beta$, with $s<1$.

Protease inhibitors need a different modelling, since they reduce infection of new cells but do not block production of viruses from cells already infected and model (1) must be suitably modified (Craig, and Xia, 2005).

A more complex model was presented in (Wodarz, and Nowak, 1999) and augmented in (Wodarz and Nowak, 2000): it offers important theoretical insights into immune control of virus based on treatment strategies, which can be viewed as a fast subsystem of the dynamics of HIV infection.

The final model of Wodarz and Nowak is mathematically described by:

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv \\ \dot{y} = \beta xv - ay - pyz \\ \dot{v} = ky - uv \\ \dot{w} = cxyw - cqyw - bw \\ \dot{z} = cqyw - hz \end{cases} \quad (2)$$

Two differential equations are added to (1) for describing the dynamics of precursors of cytotoxic T-lymphocytes CTLp (w), responsible of the development of an immune memory, and effectors of cytotoxic T-lymphocytes CTLe (z). This model can discriminate the trend of the infection as a function