A Multi-agent System for the Modelling of the HIV Infection

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Abstract. The mathematical tool was used for a long time to model the dynamics of the populations, at present approach of modeling Multi-agents seem to be promising in the views of its capacity to master the complexity of the studied systems. In this work we try to model the population of cells occurring during the infection by the virus of the human immunodeficiency (HIV) to show the efficiency of the approach Multi-agents by comparing with the mathematical approach. The obtained results allowed to bring to light the behaviour and the interactions between the various cells studied in agreement with the biological reports.

Keywords: Simulation Multi-Agents, dynamics of the populations, the infection HIV, the virtual community, bio-informatics.

1 Introduction

The modeling became indispensable for the study of the complex phenomena following the example of the dynamics of the populations. In this sense the mathematical modeling was for a long time the used approach. Recently, the approach of modeling Multi-agents began to be particularly used in the study of the dynamics of the populations relative to the cellular biology so allowing exceeding certain limits of the mathematical approach. This work concerns the study of the dynamics of a population constituted by cells occurring during an infection by the virus HIV. It is the problem which was studied widely mathematically [1] [2].

2 Dynamics of the Populations

The constituent individuals of any population are in a perpetual dynamics where each carried out the life cycle. Consequently all the population evolves in the time and in the space. Today we try to explain biological phenomena to a cellular level, with all the complexity of the interactions between cells, to do it we are going to use the approach Multi-agents which allows modeling the evolution of the phenomenon studied from the elementary behaviour of the various agents.

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2.1 Mathematical Modeling

The research in dynamics of the populations is not recent. In 1790 there was a mathematical model of Malthus [3] the exponential growth of a population, then in 1838 the model with logistic growth of Verhulst [4] was proposed. These two models describe the evolution of a homogeneous population, but in 1925 the famous system prey-predator of Lotka-Volterra [5], [6] was the first model describing the evolution of two interacting populations and on which various models were proposed to today. However the mathematical approach possesses certain limits as we try to surmount by the approach multi-agents.

2.2 Modeling by the Multi-agent Approach

The Multi-agents approach is suited well to the study of the complex systems constituted by several entities in interaction. It consists in representing every entity by an agent, then in developing the system with time.

The evolution of different agents with their basic actions and interactions that link will bring out the increase of the phenomenon studied with the appearance of behaviours and unanticipated events [8].

This approach with its low degree of abstraction allows to approach the model in the reality where every agent moves, reproduces, interacts and reacts with the changes of his environment. The most important are that the agents are distinguished some of the others and every agent is marked as could be a natural being because he can be followed at any time during his evolution. So, the addition or the retreat of an agent or of a set of agents is easy [7].

3 Infection by the HIV

An immunizing reaction is mainly expressed by the actions of cells lymphocytes called CD4 and CD8. CD4 lymphocyte produced by the Thymus is responsible for the coordination and the activation among others lymphocytes cytotoxiques CD8. This cell CD4 is subject to the infection by the virus HIV which considers them as an adequate environment to carry out its cycle of proliferation. Thus the destruction of CD4 by the HIV paralyzes the immunizing defense to its source [9].

The phenomenon of the infection by the AIDS virus thus takes place in three stages:

1 - Firstly infection: lasts from 3 to 8 weeks is characterized by a fast diminution of lymphocytes CD4 caused by an increase of the viral load.
2 - The asymptotic phase: its duration is of around ten years during which the immune system maintains a state of balance between the number of the CD4 and the viral load.
3 - It is the phase in which the immune system is depressed because of the fast decrease of lymphocytes CD4 (less of 200 / mm3).

3.1 Mathematical Model

We are interested in this study by the 3D model which is the basic model and the simplest of HIV infection. It is only interested in the evolution of three classes of cells which are CD4 cells (T), CD4 lymphocytes infected by the virus recorded (T *) and finally the virus (V).

The phenomenon is modeled by the following equations [10], where T', T*'and V' indicate respectively the variation rates in density of CD4 cells, infected CD4 cells and virus populations:

$$\begin{cases} T^{'} = s - \delta T - \beta TV \\ T^{*'} = \beta TV - uT^{*} \\ V^{'} = kT^{*} - cV \end{cases} \quad (1)$$

Table 1. Parameters list of the 3D model

Parameters	Definition
S	Production of CD4 cells by thymus
δ	Mortality rate of CD4 cells
β	Virus infectivity
μ	Mortality rate of infected CD4 cells
κ	Production rate of virus
c	Mortality rate of virus

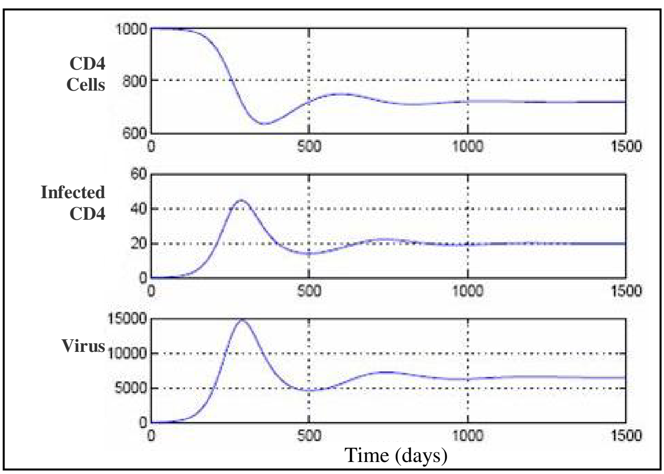

Fig. 1. Results of the mathematical model [9]

Lymphocyte CD4 cells are produced by the thymus with a constant rate equal to S cells in some blood of one mm3 in a day, and die with a rate of natural mortality equals to δ cells in a day.

The population of lymphocytes CD4 also loses a number of cells which are transformed in infected CD4 cells because of the infection by the virus with a rhythm of βTV where β represents the infectivity of the viruses HIV which is the probability that a meeting between CD4 and HIV is infectious.

The transformation rate of CD4 cells on infected CD4 is the rate of production of the last, dying with a natural mortality rate equal to μ cells per day. An infected CD4 produces a number of viruses with a rate of K Virus HIV a day, these viruses die with a natural mortality rate equals to C virus a day.

This mathematical model allows giving the following results (Fig.1), which represents the phase of firstly infection and the asymptomatic phase in the process of the infection:

3.2 Multi-agents Model

In our case, the objective consists in creating a virtual environment in which various agents evolve and interact between them. It is an environment in 3 dimensions corresponds to 1 mm3 of the blood.

We used Mad-kit platform (Multi-Agents development kit) to create Three classes of reactive agents feigning the studied cells (The agents cells CD4, the agents infected cells CD4 and the agents virus HIV).

The various agents and the interactions which connect them are represented in the figure Fig.2:

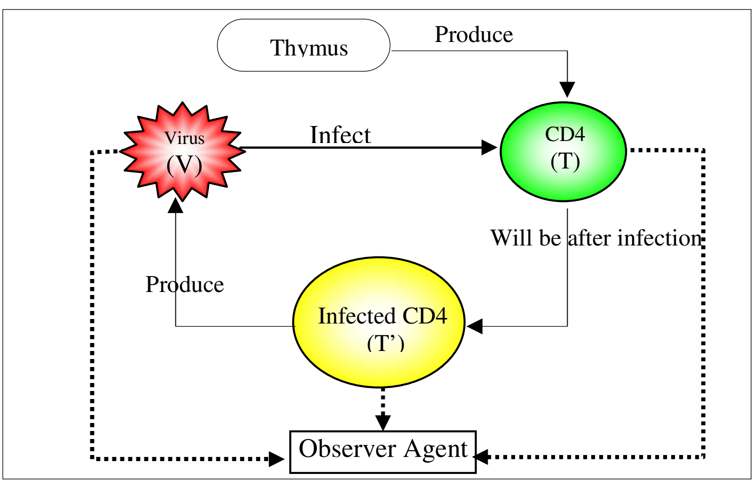

Fig. 2. Interactions in the Multi-agent system

This model Multi-agents is closer to the reality than the mathematical model, which is incapable to express the phenomenon of meeting (contact in the biological sense) between a virus and a CD4 cell.

Effectively, in the mathematical model, the number of the produced infected CD4 agents is calculated by multiplying the total number of the possible meetings between the viruses and the infected CD4 (which is equal to T*V) by the parameter β which does not describe faithfully the phenomenon.

In other words, with the mathematical model a population of 100 cells CD4 and 10 viruses gives 100*10=1000 infected cells CD4 which is not so exact because in the reality this population is going to produce most 10 infected cells CD4 if we suppose that every virus infects one CD4 cell.

That returns because the mathematical approach treats the phenomenon on high-level (consider all the population) contrary to the approach Multi-agents where the treatment is made at the level of the individuals and every meeting is treated (handled) independently of the others, which allows a more exact representation of the reality.

4 Results

4.1 Evolution without Infection

In the absence of the viruses, if we suppose that the thymus produces daily 7 cells CD4, with a mortality rate δ=0,007 that is each possesses a life expectancy (cycle) of

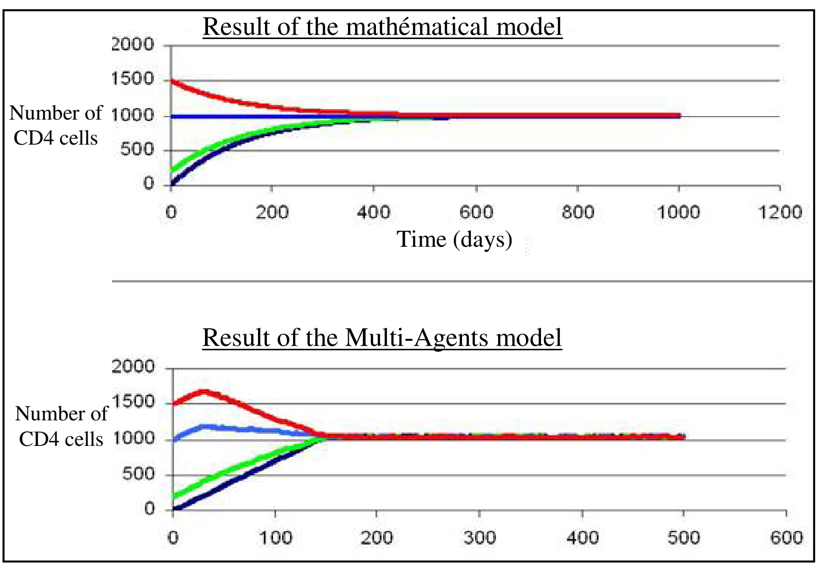

Fig. 3. Evolution of the CD4 without infection

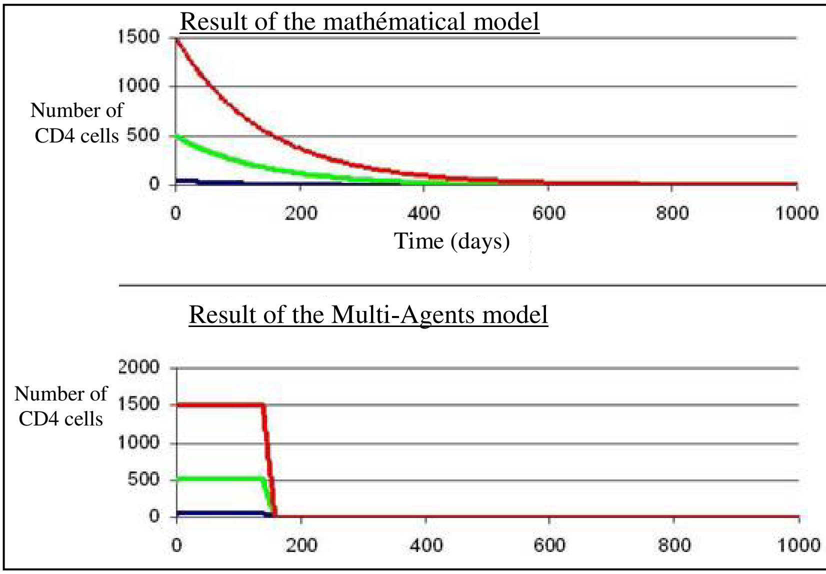

Fig. 4. Extinction of the CD4

1/δ=143days [9]. We can notice that from several random initial states: 0 cells, 200 cells, 1000 cells and 1500 cells with a random initialisation of the age of cells, the population of the CD4 will converge on 1000 cells CD4 and stabilizes around this value (Fig. 3).

We notice that the model Multi-agents converges more quickly than the mathematical model. The difference between both models also appears in the speed of extinction of a population of isolated CD4 cells that is whose daily rate of production is equals to zero (Fig.4).

The Multi-agents model shows that the population of cells CD4 disappears at once after 143 days (which is the life cycle of cells), and it independently of the initial number of the cells.

4.2 Evolution of the Infection

In an environment which represents 1 mm3 of the blood, evolve three categories of cells: infected CD4, CD4 and the viruses HIV which interact between them by feigning the phenomenon of the infection.

The average life cycles of the agents are defined as follows:

- Agents cells CD4 140 days. With a production rate equals to 7 CD4 every day.
- Agents infected cells CD4: 10 days.
- Agents virus HIV: 3 days.

We notice that the first two phases of the process of the infection are recognizable on the various curves (Fig.6):

- The phase of firstly infection is characterized by a growth of the viral population (initially little numerous) which invaded CD4 cells (initially numerous). The infection of the healthy CD4 gives infected cells CD4 which are going to produce new viruses capable of infecting of the other CD4. This growth persists to reach a rate maximal for which the reduced number of the population of the CD4 becomes a rare resource, consequently a lot of virus die without being able to infect CD4 and producing infected CD4. In that case we notice a fall of the viral load and the number of the CD4 infected.

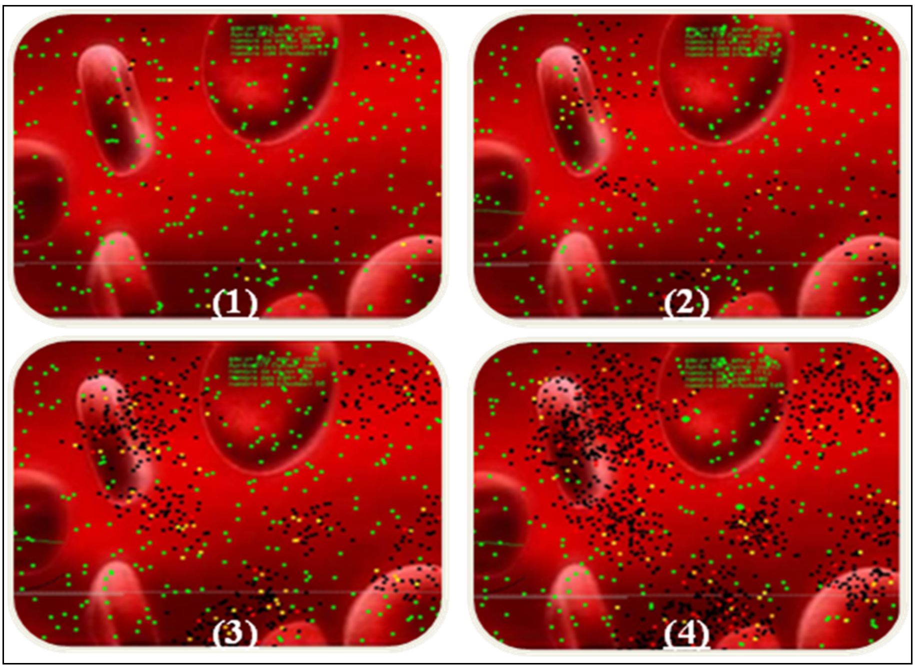

Fig. 5. Propagation of virus in the population of CD4

- The second phase of the infection which is the asymptomatic phase in which a kind of state of balance is established between the rates of the various cells.

The infectivity of the viruses plays an important role on the evolution of the phenomenon of the infection. Indeed, infectivity 100 % leads to an abrupt and fast diminution of the rate of the CD4 with regard to a lower infectivity, and this because the number of viruses produced is bigger (Fig.6).

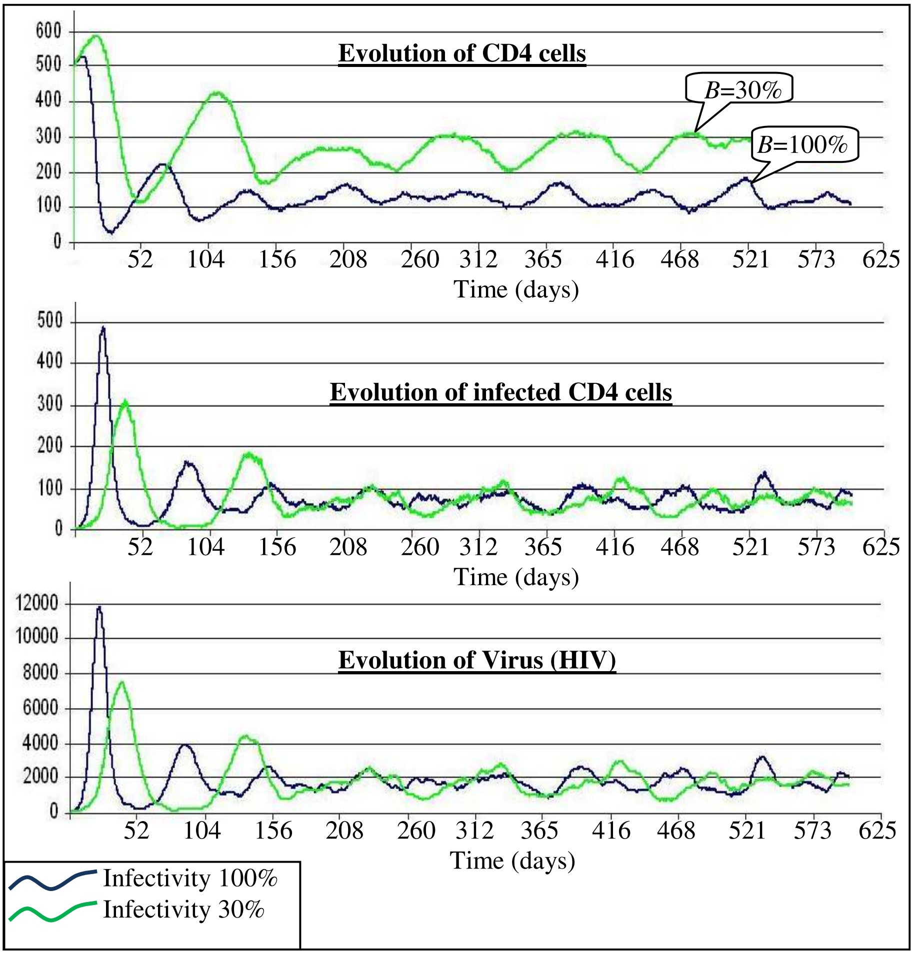

Fig. 6. Results of the Multi-Agents model

5 Conclusion

The population of the agents thus allowed to feign the studied phenomenon by reproducing the behaviour and the interactions between the various studied cells. The approach Multi-agents is suited well to the study of the dynamics of the populations thanks to its capacity to master the complexity of these systems by the direct representation of the individuals. If we define the behaviour of the other particles, the constructed model can reproduce the phenomenon of the infection and will then allow predicting its evolution.

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