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Preliminary Communication

Agent-Based Modelling Applied to 5D Model of the HIV Infection

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Abstract

This paper proposes a Multi-Agents Model to simulate the phenomenon of the infection by the Human Immunodeficiency Virus (HIV). Since the HIV was isolated in 1983 and found to be the cause of the Acquired Immune Deficiency Syndrome (AIDS) in 1984; many studies have been carried out to understand the complex dynamics between the HIV virus and the immune system. The simplest model was the 3D mathematical model. However, the complexity of this phenomenon and the diversity of cells and actors, which affect its evolution, requires the use of new approaches such as multi-agents approach that we have applied in this paper. The results of our simulator on the 5D model are promising because they are consistent with biological knowledge's on this phenomenon.

The proposed approach is well appropriate to the study of population dynamics in general and could help to understand and predict the dynamics of HIV infection.

Keywords: Multi-Agents Simulation, dynamic of the populations, the human immunodeficiency virus infection (HIV), the virtual community, bio-informatics, 3D model, 4D model, 5D model.

1. Introduction

The first Acquired Immune Deficiency Syndrome (AIDS) patients were identified in 1981 and the Human Immunodeficiency Virus (HIV) was isolated in 1983. Since

1984, the HIV is considered to be the virus that causes AIDS. Many studies and experiments have been carried out to understand and to predict the complex dynamics between the HIV virus and the immune system. [1-6].

The immune system is a coordinated set of elements (cells, molecules etc.) which are responsible for defending the body against various invasive objects. An immune response (see Figure 1) is expressed primarily by the actions of lymphocytes called CD4 and CD8 cells.

CD4 cells produced by the thymus are responsible for the coordination and activation of CD8 cytotoxic lymphocytes that destroy intrusive objects. CD4 cells are target of infection by the HIV virus, which considers them as a proper environment to carry out its cycle of proliferation. The destruction of CD4 cells by the HIV paralyzes the immune defense to its source.

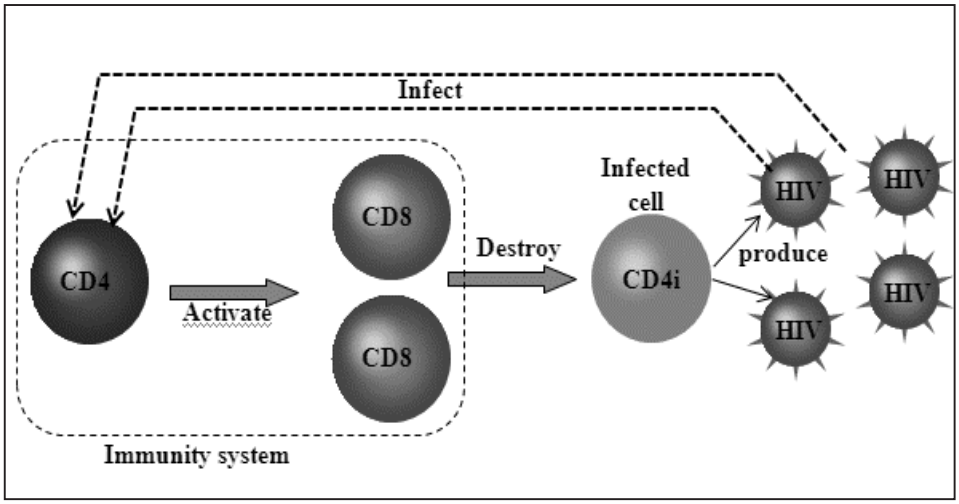

Figure 1. Action of the immune system.

The phenomenon of the infection takes place in three stages (see Figure 2):

- The acute phase: lasts from 3 to 8 weeks and is characterized by a sharp decline in CD4 lymphocytes caused by a rapid increase in viral load. This latter decrease over time and the infection is controlled.
- The asymptotic phase: it is the clinical latency period. A steady state, its duration is ten years in which HIV infects more CD4 cells. However, the immune system maintains some balance between HIV population and immune cells.
- Full-blown AIDS: It is the phase in which the immune system is depressed because of the fast decrease of CD4 lymphocytes (less of 200 / mm^3), complicated phenomena involved at this stage that is why the studies concern only the two first phases.

This work deals with the dynamics of a population of cells involved in the infection by the HIV. The purpose is the early detection of potential treatment failure in patients infected with the virus and thus improves guide treatments.

In a precedent work [7], we presented a 4 D model, which concerns the dynamic of 4 types of cells. In this paper, we are interested in the 5D models, which model the dynamic of 5 types of cells to approach better the biological reality.

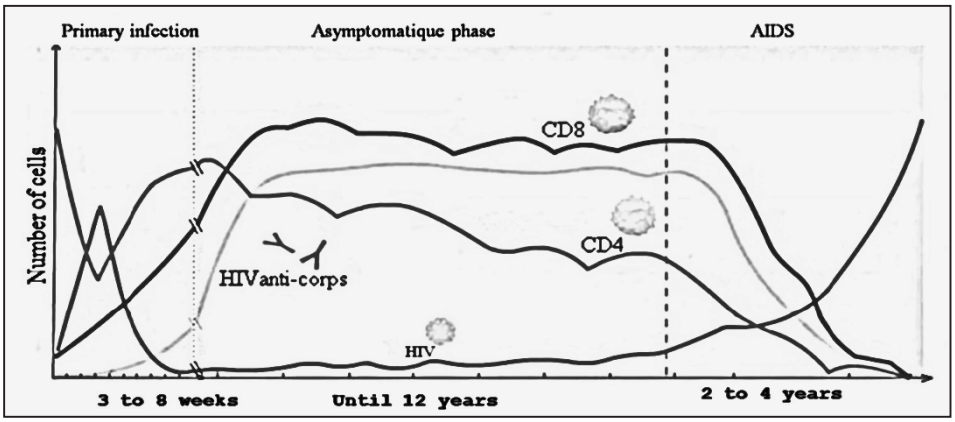

Figure 2. Evolution of the biological phenomenon.

The mathematical modeling was used for a long time to study the complex phenomena and the effectiveness of this approach is demonstrated and several mathematical models treat the dynamics of this phenomenon. Daniel Bernoulli [8] proposed the earliest mathematic model in medicine in a work dating from 1766, offering a model to estimate the benefits of smallpox inoculation.

Recently, the Multi-Agents Modeling approach began to be particularly used in the study of the dynamics of the populations relative to the cellular biology in order to overcome some limits of the mathematical approach.

The rest of the paper is structured as follows: In section two, population dynamics is briefly presented. Next, a brief description of the mathematical modeling is given. Then, the Multi-Agent Model approach is provided. Section 5 includes the 5D HIV dynamic model and afterwards, experimental results and discussion are given. Finally, in the sixth section conclusion is presented.

2. Populations dynamics

The population dynamics is the science aiming to study the evolution of individuals of the population through time and space and the interaction between them, in order to understand the overall behavior of the population.

In 1790, Malthus [9] proposed a mathematical model of the exponential growth of a population. Then, in 1838, Verhulst [10] adopts the model with logistic growth. These two models describe the evolution of a homogeneous population. Furthermore, in 1925 the famous system prey-predator of Lotka-Volterra [11], [12] was the first model describing the evolution of two interacting populations on which different models have been proposed until now.

2.1. The mathematical models

2.1.1. The exponential growth

As a consequence of the extreme poverty that has affected many English families, Malthus [9], investigating the causes of this trend, asked: what would be the natural increase of the population if it evolved without any limiting factors? He found that the population is growing exponentially and that the size of the population in each period is a geometric sequence with a ratio equal to λ (see Figure 3). If P_0 is the initial population size, the population at the nth period is:

$$P_n = P_0\lambda^n = P_0 e^{nLn\,\lambda} \qquad (1)$$

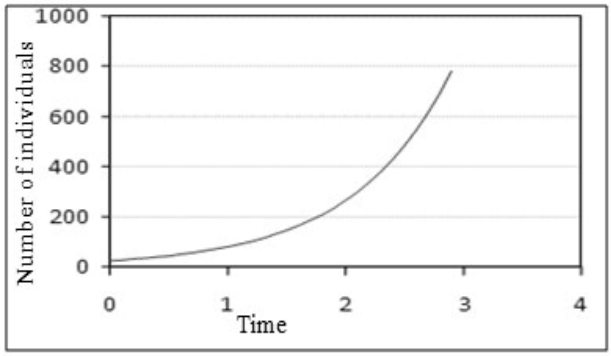

Figure 3. The exponential growth.

We can see on Figure 4 that the amount of change (the rate of increase) of the population dP/dt changes linearly with the size of the population.

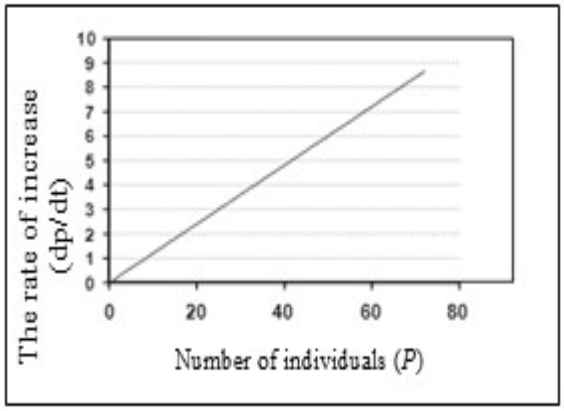

Figure 4. The speed of population growth.

2.1.2. Logistic growth

In 1838, Verhulst [10] noted that the Malthus model [9] was not valid for a large number of periods. The growth rate, assumed to be constant (and therefore the rate of birth and death), does not depend on the size of the population, which leads to an exponential growth. In reality, the problem is caused by the negligence of the density of the population, that is to say the number of individuals per unit area (and therefore the amount of resources reserved for individuals), which affects positively or negatively both the birth and the mortality rate.

Auto-limitation of a population is the phenomenon where the growth rate decreases with density. This decrease goes on until it reaches equilibrium between birth and mortality rates, i.e., density-dependent (see Figure 5). The size of the population is at this point called the limit capacity of the environment noted K.

$$P_{n+1} = P_n + \lambda P_n \left(1 - \frac{P_n}{K}\right) \qquad (2)$$

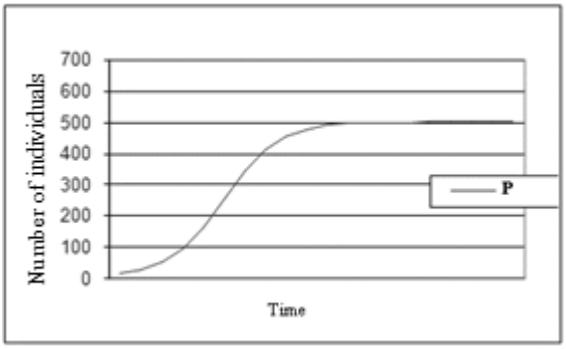

Figure 5. Logistic growth.

We note in Figure 6 that the variation in the number of individuals (rate of change) is not constant, it reaches a maximum for a number of individuals = $K/2$. For a number of individuals more important than K the growth rate becomes negative.

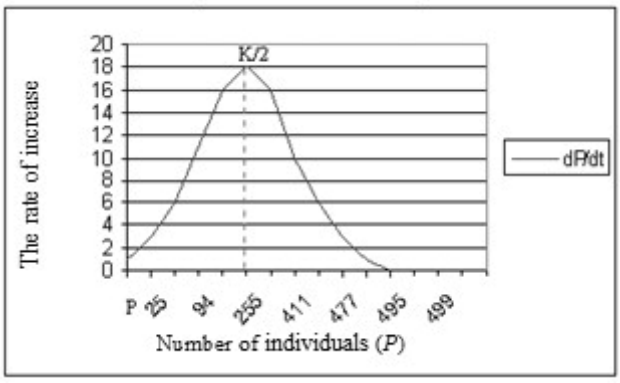

Figure 6. The phenomenon of auto-limitation.

2.1.3. Interaction modeling (the Lotka-Volterra equation)

This is the golden age of the population dynamics modeling. Works do not apply to a single population anymore, but to a set of population (see Figure 7) sharing the same environment.

For example, a system of two populations (prey and predator) is modeled by the equation of Lotka-Volterra [11], [12], which is the basis for most current models of interaction.

$$\begin{cases} X'(t) = \alpha X(t) - \alpha X(t)Y(t) \\ Y'(t) = -bY(t) + \beta X(t)Y(t) \end{cases} \quad (3)$$

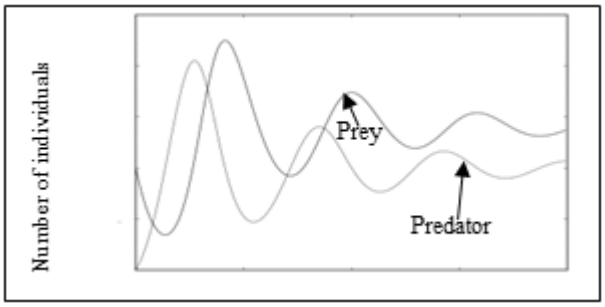

Figure 7. The prey- predator system.

In the presence of two species, the number of prey increases by default, except in the case of predation where a group of individuals will be lost. Following the same pattern, the number of predators decreases by default (mortalities) except in the presence of prey where predation will ensure their survival.

3. Mathematical models in HIV dynamics

The mathematical modeling of a phenomenon requires that all entities and relations between them are known and clearly defined. Then, a mathematical model is built by using initial axioms and equations that rely model entities. Often, there are systems of Ordinary Differential Equations (ODE) that are used to study dynamics of infectious diseases and especially HIV dynamics. Several mathematical models have been developed and, as a result, new branches like mathematical epidemiology have emerged.

However, the mathematical models can becoming complex and with higher degree of non-linearity, and finding solutions may be impossible. In this, case, solutions can be approximated by using numerical simulations with fixed parameters [13]. Several researchers have developed and used mathematical models in research in HIV/AIDS. The initial mathematical models was developed by May, Anderson et al. [14–16] Very soon after the discovery of the virus.

Then, many researchers have invested this area of research extensively. While refining the parameters come into play in the phenomenon of the virus inoculation, its

spread and transmission modes (sex, blood, etc.), as well as the phenomenon of the onset of AIDS. The mathematical models offer a set of formal tools to track all of these steps.

The simplest one involves three types of cells, called mathematical 3D model of Perelson and Nelson [3]. In [17] E. Jones and P. Roemer present a mathematical model using ODE for analysis and simulation of HIV dynamics during the initial stages of infection. They examine the Three Component Model (3CM) and prove the existence of solutions.

Kinetics modeling permits to understand the course of infection. Thus, it is a good help to predict the behavior and to design and optimize the antiviral treatment and drugs. A large number of mathematical models of HIV dynamics have been proposed [18-23].

3.1. Limitations of the mathematical approach

We can see in recent years, that most papers published in major journals of biology are mathematical models. This is particularly true in the field of ecology and environmental sciences. Modeling the systems through a mathematical approach is a widely used method as it has the advantage of being a universally understood language able to describe the evolution of a population of individuals in consideration of the different types of interaction that may exist between them.

Nevertheless:

- The constructed mathematical model is a global view of the system, meaning that it describes the evolution of all individuals regardless of elementary behaviors, i.e., the constructed model is a model that describes the average behavior of a system and therefore the influence of individuals of a species with low presence will not be taken into account.
- The introduction of a new population implies the modification of the whole system.
- Mathematical models are models of high level of abstraction, which often lose the biological sense.
- Constructed models are generally restricted to a set of hypotheses. Malthus model, for example, describes the exponential growth of a supposed population found in an environment that offers unlimited abundance of resources, something untested in practice.
- The mathematical approach has some limits (complexity of the equations, difficulty in updating the model, abstract models …).

Nowadays, other approaches focused on IT tools can provide alternatives to mathematical methods. These tools take advantage of the flexibilities of programming and technological advances that make computers more and more efficient.

In addition, the software engineering, the programming platforms, the modeling, and the simulation environments are becoming more powerful, stable and performants. The multi-agent systems become increasingly used in the field of modeling.

4. Multi Agent Systems Models

An agent is an autonomous physical or abstract entity, which is able to act on itself and on its environment and whose behavior is the result of his observations, his knowledge, and interactions with other agents [24].

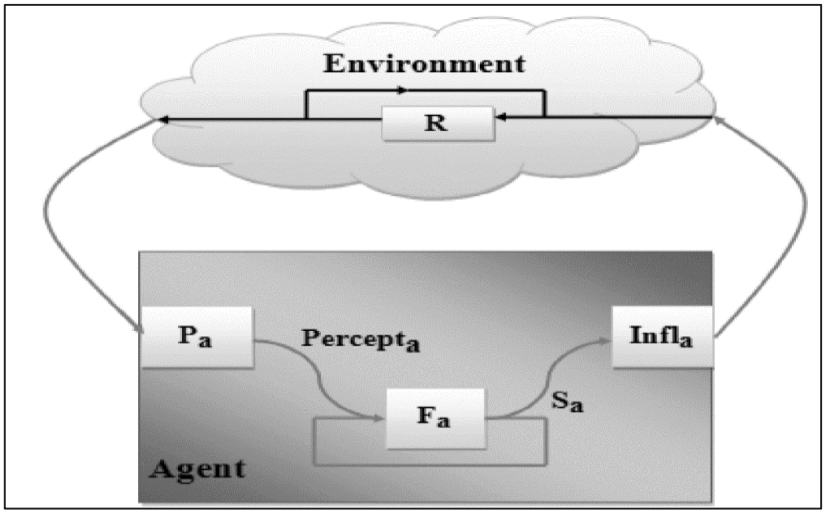

Figure 8. Perception-Reaction Agent.

A multi-agent system is a distributed system consisting of a set of agents. The interactions between those agents can be made in three different ways:

- Thanks to a shared memory or blackboard.
- Through messages.
- Through the environment perceived by the agents.

There is several ways of representing and formalizing an agent. J. Ferber [24-27] represents a system multi-agent by the couple < A , W > where A is an agent and W an environment as described figure 8.

$$A = (P_a, Percept_a, F_a, Infl_a, S_a) \qquad (4)$$

$$W = (E, \Gamma, \Sigma, R) \qquad (5)$$

With :

P_a: function of perception of the agent.

Percept $_a$: A set of stimuli and feelings that an agent can perceive.

F_a: function of behaviour of the agent.

$Infl_a$: function of action of the agent.

S_a: A set of internal states of agent.

And:

E: space in which the agent evolves.

Γ: space of influences produced by the agent.

S: state of the environment.

R: law of evolution.

The Multi-Agents approach is well suited for the study of complex systems constituted by several entities in interaction. It consists in representing every entity by an agent, then in developing the system over time. The evolution of different agents and the basic actions and interactions that link them will bring out the dynamic of the studied phenomenon with the appearance of behaviors and unanticipated events.

This approach with its low degree of abstraction allows to approach the model from the reality, where every agent moves, reproduces, interacts and reacts with the changes of its environment. The most important point is that every agent is different from another and that every agent is marked and can be followed at any time during its evolution. Consequently, the addition or the retreat of an agent or of a set of agents is an easy operation.

In the literature, there are few works concerning the application of the MAS formalisms and concepts to model infectious diseases. In [28-29] the authors present, a complete MAS formalism called OPERAS and its application in multiple domains such as biology. It seems that application of this system in VIH modeling is suitable. Other works of MAS models of HIV dynamics have been proposed [30-32].

Our research team works for many years and proposed MAS modeling of 3D and 4D HIV dynamic models [7, 32].

5. The 5D HIV Model

In this study, we are interested in the 5D model, which describes the dynamic of five types of cells: CD4 cells, infected CD4 cells, HIV virus and the CD8 lymphocytes cells (noted TCTL for Cytotoxic T-Lymphocytes) with its two types: naive CD8 cells and active CD8 cells. The active CD8 cells are responsible for the destruction of the infected CD4 cells (virus-producing cells) [2].

5.1. The 5D mathematical model

The 5D model is given by equations (6) [9], where $\boldsymbol{T'}, \boldsymbol{T^{*\prime}}, \boldsymbol{T'ctl}$ and $\boldsymbol{V'}$ indicate, respectively; the variation rates in the density of $\boldsymbol{T}, \boldsymbol{T^{*}}, \boldsymbol{Tctl}$ and viruses $\boldsymbol{V}$. CD4 lymphocyte cells are produced by the thymus at a constant rate equal to $\boldsymbol{s}$ cells a day in 1 mm^3 of blood, and die at a rate of natural mortality equals to $\boldsymbol{\delta}$ cells in a day.

The population of CD4 lymphocytes loses some 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, i.e., the probability that a physical contact between CD4 and virus HIV is infectious.

The transformation rate of CD4 cells on infected CD4 is the rate of production of this last one. Infected CD4 cells die at a natural mortality rate equal to u cells per day. An infected CD4 produces a number of viruses at a rate of K Virus HIV a day, these viruses die at a natural mortality rate equals to c virus a day.

The CD8 lymphocytes are cells of the immune system, they have a toxic capacity that enables them to play a defensive role and destroy the infected CD4 cells (and intrusive objects in general).

$$\begin{cases} T' = s - \delta T - \beta TV \\ T^{*'} = \beta TV - uT^* - qT_{ctla}\,T^* \\ T^*_{ctln} = \lambda - wT^*\,T_{ctln} - \alpha T_{ctln} \\ T'_{ctla} = wT^*\,T_{ctln} + aTT^*\,T_{ctla} - \gamma T_{ctla} \\ V' = KT^* - cV \end{cases} \quad (6)$$

The table below describes the parameters of this model.

Parameters	Definition
s	Production of CD4 cells by thymus
δ	Mortality rate of CD4 cells
β	Virus infectivity
u	Mortality rate of infected CD4 cells
q	Cytotoxity of the active CD8 against the infected CD4
w	Activation rate of naives CD8.
λ	Production rate of the naïve CD8 by the thymus
a	Proliferation Rate of the active CD8
α	Mortality rate of naive CD8 cells
K	Production rate of virus
c	Mortality rate of virus
γ	Mortality rate of active CD8

TABLE 1. PARAMETERS LIST OF THE 5D MODEL

The thymus produces naive CD8 cells (Tctln) with a rate λ cell per day. After the contact with infected CD4 (T^*), the naive CD8 become active with a rate $w\,T^*\,T_{ctln}$ where w represents the rate (probability) of activation of naive CD8 following this physical contact.

The active CD8 cells (T_{ctla}) proliferate at a rate $aT\,T^*T_{ctla}$ proportional to the number of infected CD4 cells, active CD8 and healthy CD4 cells. α is the mortality rate of the naive CD8 cells (T_{ctln}).

The active CD8 destroy the infected CD4 with a rate of qT^*T_{ctla} where q represents the cytotoxity of the active CD8 cells. In other words, it is the probability that a physical contact between an active CD8 cell and an infected CD4 cell leads to the elimination of this latter (disinfection).

This mathematical model gives the results shown in figure 9, which represents the acute phase and the asymptomatic phase in the infection process.

We notice that the number of CD4 decreases rapidly during the acute phase because of the invasion by the viruses which causes an exponential increase of the viral load. In this time, the naïve CD8 cells (T_{ctln}) start to activate rapidly (become active cells to eliminate the infected cells before they have the chance to release new viruses) which explain the decrease of the curve.

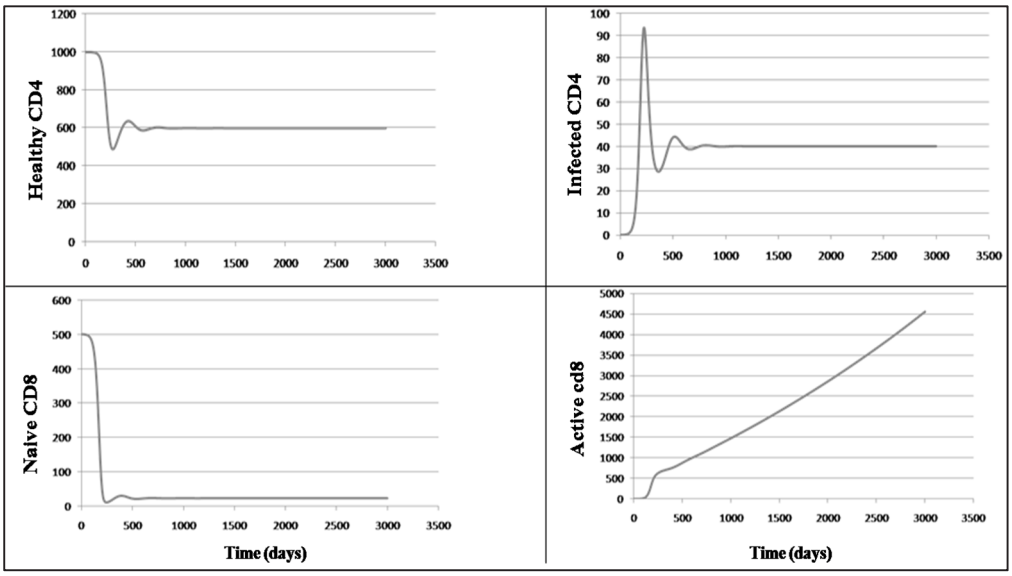

Figure 9. Results of the 5D mathematical model.

5.2. Multi-Agents Model

To model the phenomenon by a Multi-Agents System, a virtual environment was created. In this environment, various agents evolve and interact between them. It is an environment in three dimensions which corresponds to 1 mm^3 of blood. To simulate the 5 studied cells (The CD4 cells agents, the infected CD4 cells agents, CD8 naive and actives cells agents, and the virus HIV agents). Five classes of reactive agents were created. Each agent mimics the behavior of a biological cell. Simulation process of the different biological actions of the phenomenon are conducted (creation of the cells, moving in the environment, infection, production of the viruses, immune defense, etc.)

The general architecture of the simulator is given figure 10. This is the UML class diagram which describes the main classes used in the simulator and the relations between them

The observer agent (watcher) represents the environment in which agents evolve. It is necessary to run the system because in addition to the graphical display of the simulation, it is devoted to provide different information on all the other agents. For example, to find the closest CD4 agent, HIV agent must calculate the distance to all CD4 agents; hence it has to be aware of the coordination of all these agents, and the observer agent is the one to give this information. It's the same thing with the active CD8 agents: they need information about all infected CD4 agents in order to calculate the distance and find the closest one, and the observer agent is in charge of providing this information.

This Multi-Agents model is closer to the reality than the mathematical model. The mathematical model is unable to express the phenomenon of the physical contact

between a virus and a CD4 cell (the action of the infection) and between a CD8 cell and an infected CD4 cell (the action of disinfection).

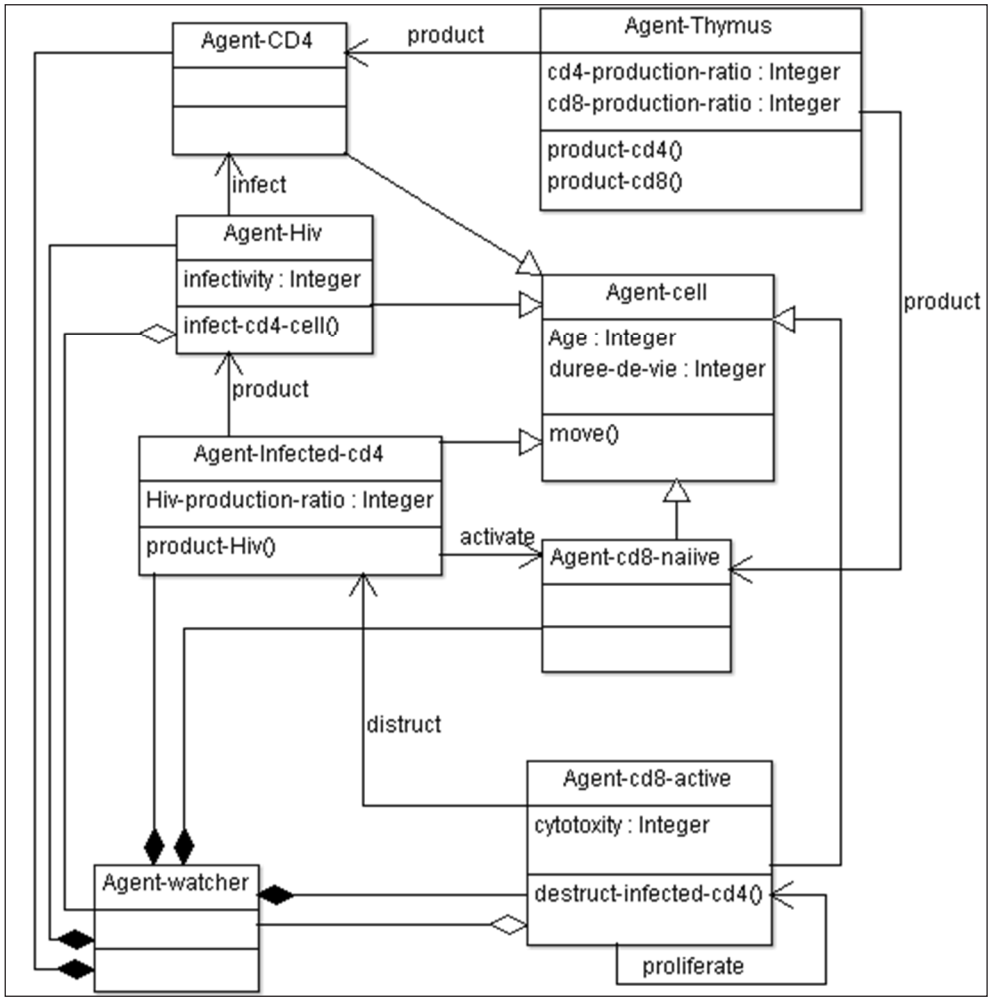

Figure 10. UML diagram class of the MAS model.

The same thing for the CD8 actives proliferation, the mathematical model estimates this value by the multiplication aTT^*T_{ctla}, i.e., all CD8 have proliferated because this model does not make any distinction between the CD8 active cells. On the contrary, in the Multi-Agents model, at every contact between an infected CD4 cell and a CD8 cell, the two cells (agents) involved are well-known; because the agents are distinguished from each other!

This is explained by the fact that the mathematical approach treats the population as a single entity contrary to the Multi-Agents approach where the processing (the execution of the agents behaviors) is done at an individual level, and where interactions between cells (agents) are treated independently, which allow representing faithfully

and accurately the biological phenomenon.

5.3. Implementation

To develop our Multi-Agents simulation we first worked with the MadKit platform but we got a memory overflow problem due to the large number of agents (thousands for each cell type especially viruses). Therefore, we developed our micro Multi-Agents platform, where we organized the cells agents in vectors and created threads to execute them. The Netlogo simulation platform seems very interesting too, and we are thinking about using it in our future work. Indeed, this platform permits to reduce consequently the time required for the development and execution. Figure 11 represents the interface of our simulator.

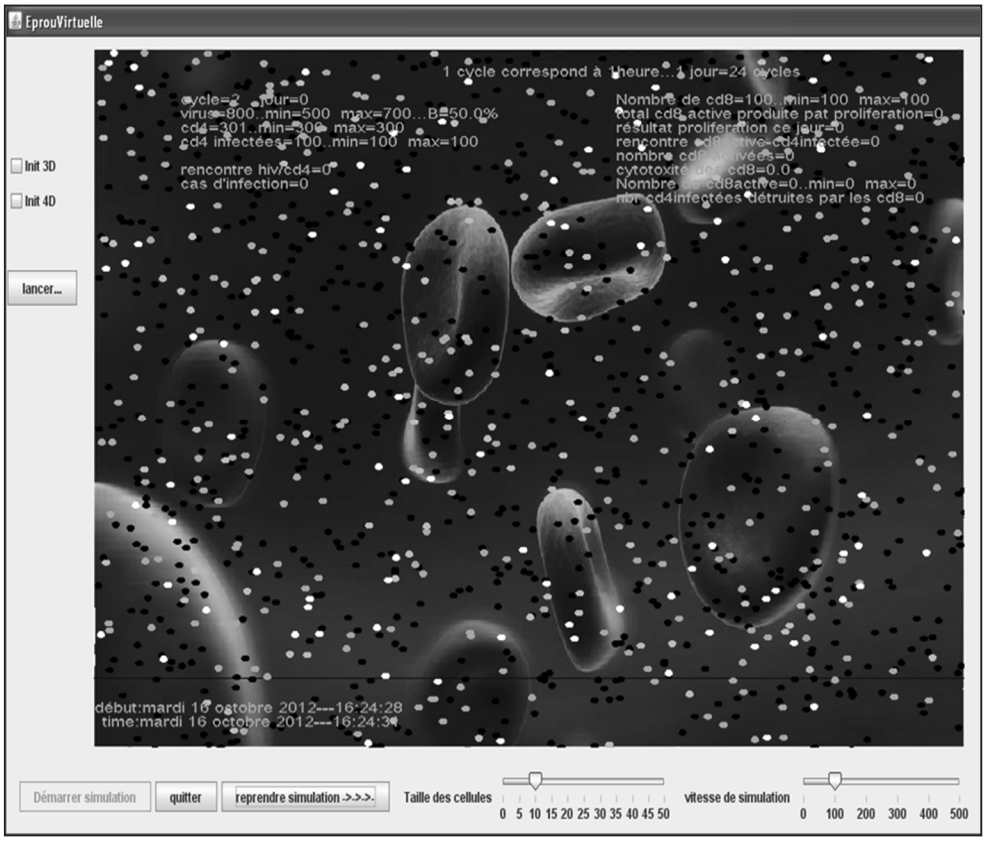

Figure 11. The interface of the simulator.

5.4. Results and discussion

The multi-agent model can reproduce the phenomenon of HIV infection. Both first phases (the acute phase and asymptomatic phase) are described in [7] with their characteristics which are consistent with biological findings.

During the infection, we notice the presence of two types of CD8 cell because the naive CD8 cells are activated after the biological contact with an infected cell. It is therefore evident that the activation rate of CD8 reaches its maximum when the number of infected CD4 is maximum i.e., during the acute phase. So during this phase we note that the number of naive CD8 cells decreases rapidly (because of the activation) and then stabilizes during the asymptomatic phase. While the active CD8 cells increase sharply during the acute phase because of the large number of the infected CD4. Figure 12 shows the results of the Multi-Agents model.

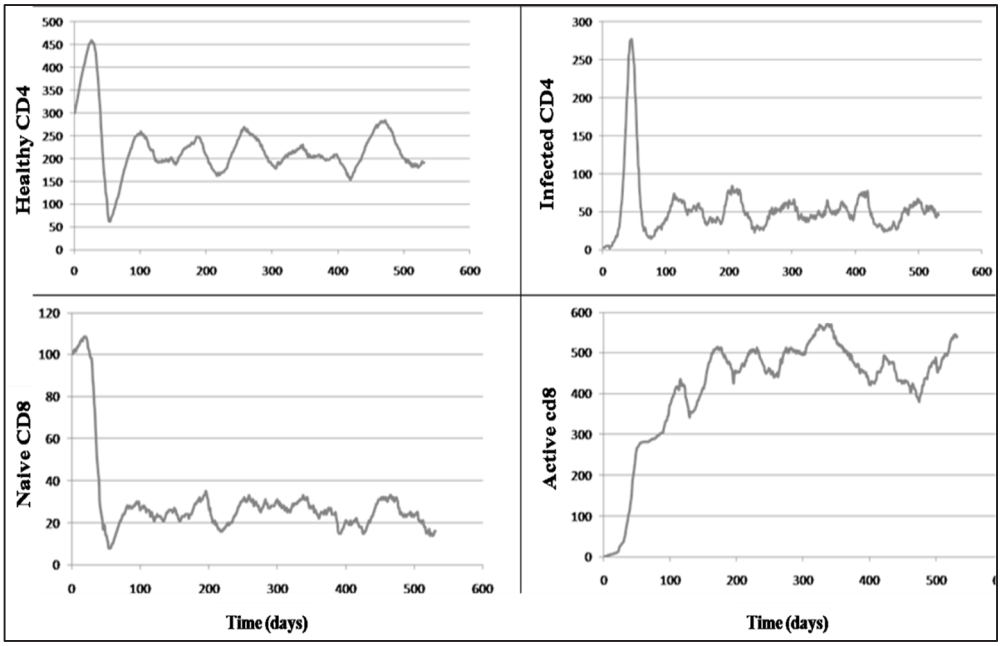

Fig. 12. Results of the Multi-Agents System for the 5D model.

We can see the relation between the naive and the active CD8 cells. At the beginning of the infection, the number of active CD8 is very low because all CD8 cells are naïve (there is not a lot of infected CD4 cells). During the acute phase, we can observe the rapid decrease of naive CD8, which become active CD8 cells.

The population of active CD8 increases significantly between the 20th and the 50th day (during the destruction of infected CD4), due to the activation of naive CD8 and to the proliferation. During the asymptomatic phase, the activation of CD8 slows down because the infection is controlled and the number of infected CD4 is reduced. These results are consistent with biological knowledge about the evolution of the phenomenon.

The 5D model gives more information about the progression of the dynamics of the HIV and this approach is better than the 4D model wish doesn't take into account the difference between the CD8 cells.

6. Conclusion

It can be concluded that the dynamics of HIV infection is well reproduced in the simulation (we speak about the two first stages of the infection). The population of agents could reproduce faithfully what is known about the phenomenon of HIV infection. Completing the model by adding CD8 cells led to results consistent with biological knowledge, especially in the acute phase and the asymptomatic phase. It is clear that no model is totally complete. Our Multi-Agents system (and the studied mathematical model) takes into account only the types of cells that seem most important, and does not model the entire details of the phenomenon.

The results encourage us to include the behavior of other types of cells and molecules, as well as to tackle the memory concern (problem of memory overflow) wish is the main drawback of this approach linked to a big number of agents, and that is a well-known problem in this kind of applications.

The Multi-Agents constructed model can reproduce the phenomenon of the infection and predict its evolution, which will enable us to diagnose patients quite early, to point out treatment failures and find better guide treatment. Moreover, it works without using blood samples which is a costly operation, both financially and ethically for the patients.

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