A Multi-Agent's Modeling for the 4D Model of hiv Dynamics

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***Abstract*—The purpose of the modeling of the biological processes is to understand better the complexity of these phenomena; using various models. The following research is an attempt to study the dynamics of the population of cells intervening during a human immunodeficiency virus (HIV) infection. This problem was mainly studied mathematically by using mathematical models which are based on the differential equations. We will use the approach of modeling Multi-agents to simulate the 4D model of this bio-process and show that the multi-agents model is more close to the real biological phenomenon than a mathematical model without underestimating the mathematical approach. The obtained results are consistent with the biological phenomenon and encouraged us to further improve the model.**

Keywords-Multi-Agents Simulation; dynamic of the populations; the human immunodeficiency virus infection; the virtual community; bio-informatics.

I. INTRODUCTION

The mathematical modeling was for a long time used to study the complex phenomena and the efficiency of this approach is not any more to be shown. However, the Multi-agents approach began to be particularly used in the study of the dynamics of the populations relative to the cellular biology so allowing exceeding some limits of the mathematical approach.

This work studies the dynamics of the population of cells concerned by the human immunodeficiency virus infection. There are several mathematical models that treat the dynamics of this phenomenon [3] [5]; the simplest is the 3D model [2] which we modeled with the multi-agents approach in [9]. We are interested in this work by the 4D model which is more complicated than the 3D model because it takes in consideration the dynamics of 4 categories of cells.

This paper begins with a small presentation of the study field; wish is the modeling of bio-process (by using the mathematical modeling). Followed by an explication of the multi-agent modeling approach and the studied biological phenomenon (the human immunodeficiency virus infection).

After that, the multi-agent system is presented with a discussion of the obtained results comparing with the mathematical model and the 3D system.

II. DYNAMICS OF THE POPULATIONS

The dynamics of the population is the science that studies the evolution of the individuals of the population in time and space as well as the interaction between them to understand the global behavior of the population.

The research field is not recent. In 1790, there was a mathematical model of Malthus [10] (the exponential growth of a population), and then, in 1838, the model with logistic growth of Verhulst [7] was proposed. These two models described the evolution of a homogeneous population; but, in 1925 the famous system prey-predator of Lotka-Volterra [1] [11] was the first model describing the evolution of two interacting populations and on which various models were proposed to today. However, the mathematical approach has some limits (complexity of the equations, difficulty in updating the model, abstract models, etc.) that we are trying to overcome by using the multi-agents approach.

III. MULTI-AGENTS MODELING 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 them will bring out the dynamic of the studied phenomenon with the appearance of behaviors and unanticipated events [6].

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 is that the agents are different than the others and that every agent is marked and can be followed at any time during its evolution. So, the addition or the retreat of an agent or of a set of agents is an easy operation [8].

IV. INFECTION BY THE HUMAN IMMUNODEFICIENCY VIRUS

An immune reaction is mainly expressed by the actions of lymphocytes cells called CD4 and CD8. CD4 lymphocyte produced by the Thymus is responsible of the coordination and the activation of cytotoxic lymphocytes CD8. This CD4 cell is an infection subject by HIV virus which considers them as an adequate environment to carry out its cycle of proliferation. So, the destruction of CD4 by the HIV paralyzes the immune defense to its source [4].

The phenomenon of the infection takes place in three stages (see Figure 1):

- Primary infection: lasts from 3 to 8 weeks, it is characterized by a fast diminution of lymphocytes CD4 caused by an increase of the viral load,

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followed by a decrease of the viral load what allows increasing the number of the cd4.

- The asymptotic phase: its duration is of around 10 years during which the immune system maintains a state of balance (stability) between the number of the CD4 and the viral load.

- AIDS: It is the phase in which the immune system is depressed because of the fast decrease of CD4 lymphocytes (less of 200 / mm3).

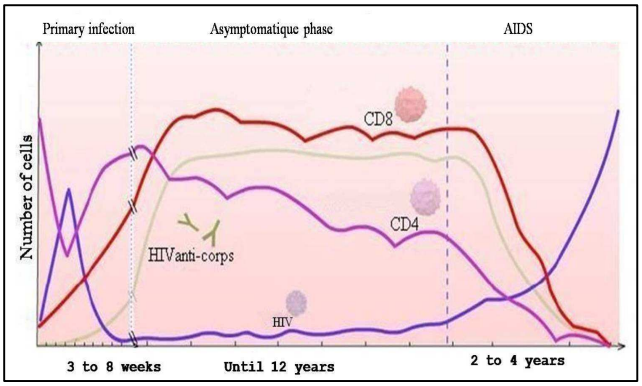


Figure 1. evolution of the biological phenomenon

A. *The 4D Mathematical Model*

We are interested in this study of the 4D model which treats 4 types of cells: the cd4 lymphocytes (T), the viruses HIV (V), the CD4 lymphocytes infected by the viruses (T^*) and the CD8 lymphocytes (T_{CTL} for Cytotoxic T-Lymphocyte).

The phenomenon is modeled by the following equations [4], where $T^{'}, T^{*'}, T^{'}_{CTL}$ and $V^{'}$ indicates respectively the variation rates in density of CD4 cells, infected CD4 cells CD8 cells and the virus populations:

$$\begin{cases} T^{'} = s - \delta T - \beta TV \\ T^{*'} = \beta TV - uT^{*} - qT_{ctl}T^{*} \\ T^{'}ctl = \lambda + aTT^{*}T_{ctl} - \alpha T_{ctl} \\ V^{'} = kT^{*} - cV \end{cases} \quad (1)$$

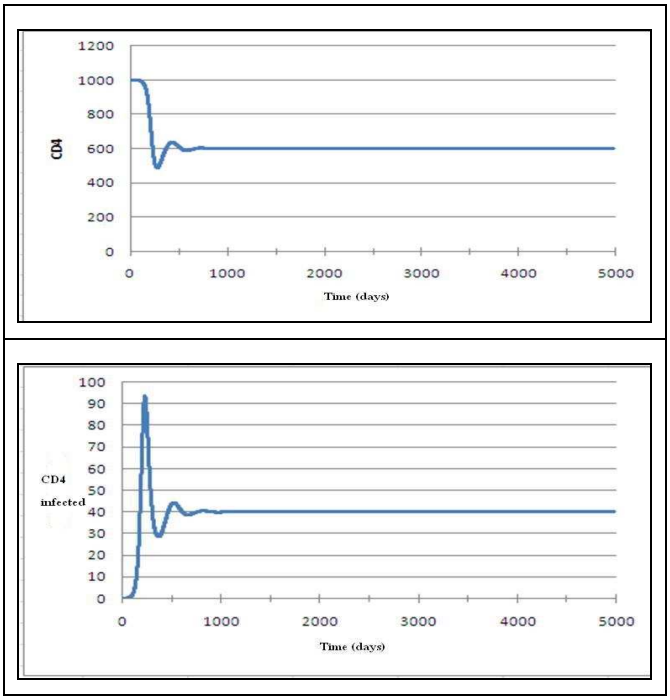
TABLE I. PARAMETERS LIST OF THE 4D MODEL

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 CD8 against the infected cd4
λ	Production rate of the cd8 by the thymus
a	Rate of proliferation of the cd8
α	Mortality rate of CD8 cells
k	Production rate of virus
c	Mortality rate of virus

CD4 lymphocyte cells are produced by the thymus at a constant rate equal to s cells a day in 1 mm^3 of blood, and die at a rate of natural mortality equals to δ cells in a day.

The population of CD4 lymphocytes loses also 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 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, dying 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.



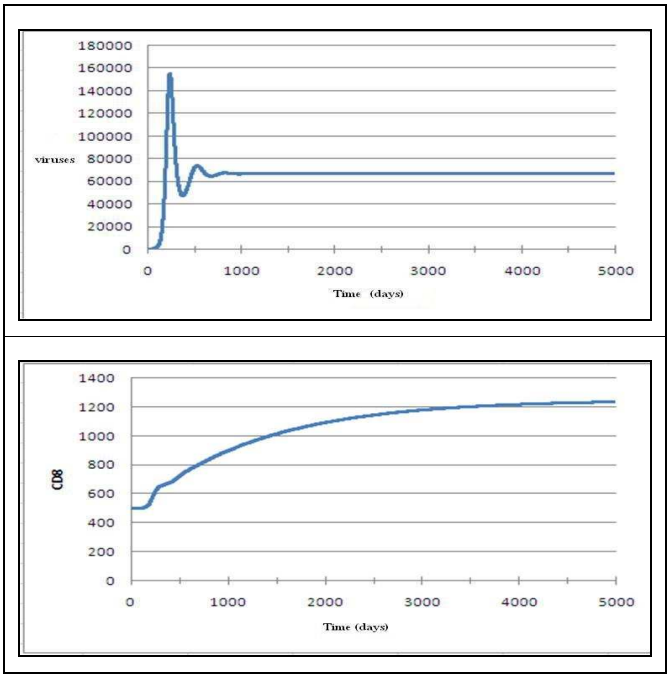


Figure 2. Results of the mathematical model [4].

The CD8 lymphocytes are cells of the immune system, they have a toxic capacity that enables them to play a defensive role to destroy the infected cells cd4 (and foreign objects in general).

The infected CD4 cells are destroyed by the CD8 at a rhythm of qTT_{CTL} where q represents the cytotoxity of the CD8 cells, in other words, the probability that a contact between a cd8 cell and a cd4 infected cell leads to the destruction of this second.

The CD8 cells are produced by the thymus with a constant rate = λ cells per day, and die with a death rate = α cells per day. During their defensive intervention, the cd8 are proliferated with a rhythm = $aTT^{*}T_{CTL}$ proportional to the number of cd4, infected cd4 and the current number of the cd8 cells.

This mathematical model gives the following results (Figure 2), which represents the phase of the primary infection and the asymptomatic phase in the process of the infection.

We notice that the number of the cells CD8 increases during the phase of the primary infection because of the proliferation of the cells, then it starts to stabilize during the asymptomatic phase after the stability of the rates of the CD4 and of the infected CD4 cells.

B. *Multi-agents Model*

To simulate the phenomenon by a Multi-agents system, we created a virtual environment in which various agents evolve and interact between them. It is an environment in 3 dimensions that corresponds to 1 mm^3 of the blood.

We created four classes of reactive agents feigning the studied cells (The CD4 cells agents, the infected CD4 cells agents, CD8 cells agents and the virus HIV agents (Fig. 3). Each agent reproduces the behavior of a cell; we find the different biological actions of the phenomenon (creation of the cells, movement in the environment, infection, production of the viruses, immune defense, etc.).

In each class, there is a population of agents wish move in the environment. Hiv agents move in the environment, find the closest cd4 agent and infect it if possible.

Infected CD4 agents move in the environment and produce new HIV agents. CD8 agents move in the environment, find the closest CD4 infected agent and destroy it if possible then proliferate to create new agents.

The thymus Agent represents the thymus; his role is the production of CD4 and CD8 agents.

The observer agent is required to execute the system because it provides information's about all agents. For example, to find the closest cd4 agent the HIV agent must calculate the distance from all cd4agents, so he must have the coordinates of all these agents, it is the agent observer who gives this information.

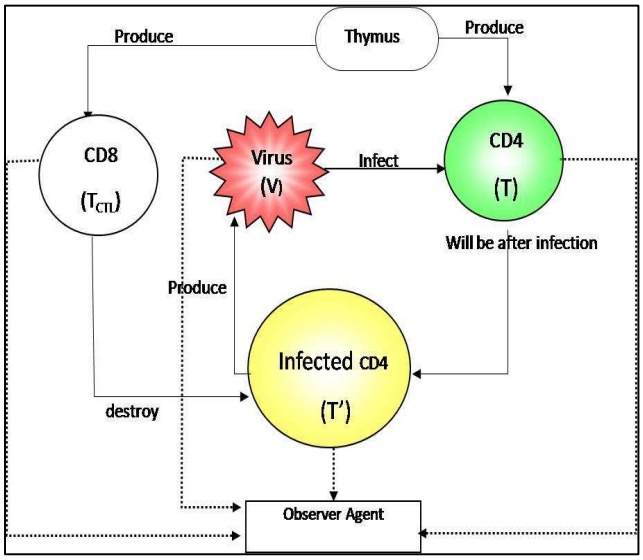


Figure 3. Interactions in the Multi-agent system.

This model Multi-agents is closer to the reality than the mathematical model, which is unable to express the phenomenon of meeting (contact in the biological sense) 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 defense or the destruction of the infected CD4).

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

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In other words, by means of the mathematical model, a population of 100 CD4 cells and 10 viruses gives 100*10=1000 infected CD4 cells which are not so exact because in the reality this population produces in maximum 10 infected cells CD4 if we suppose that every virus infects one CD4 cell [9].

The same thing for the number of the infected CD4 cells eliminated by the cd8 cells; the total number is calculated by multiplying the number of the possible contacts between the CD8 and the infected CD4 cells (which is equal to $T_{CTL}T^*$) by the parameter q.

It is obvious that if there are 100 CD8 cells and 10 infected CD4 cells, the number of destroyed cells will be 10*1000 = 1000 cells if we suppose that q=1 while there were only 10 cells at the beginning.

The number of the CD8 is multiplied during the destruction of the infected CD4 cells (by proliferation), consequently it depends on the number of the CD4, infected cd4 and CD8 more exactly depends on the number of the contacts between cd8 and cd4 infected. The mathematical model estimates this value by the multiplication aTT^*T_{CTL}, i.e., all cd8 are proliferated because it does not make a distinction between the cd8 cells contrary to the Multi-agents model where for each contact between cd4-infected and CD8 the two cells (agents) members of this phenomenon are well-known because the agents are distinguished from each other!

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 each contact between cells is treated independently of the others, which gives a more exact representation of the reality.

V. RESULTS

A. *Evolution without infection*

In the absence of the viruses or foreign dangerous objects, the number of the cells cd8 remains constant. If we suppose that the thymus produces daily 1 CD8 cell, at a mortality rate δ=0,002, that means that the lifespan of cells is 1/ δ =500 days [4]. We can notice that from several random initial states: 0 cells, 1000 cells and 1500 cells with a random initialization of the age of cells (between 0 and 500 days to have a homogeneous population wish is close to the reality), the population of the CD8 will converge on 500 CD8 cells and stabilizes around this value (Fig. 4).

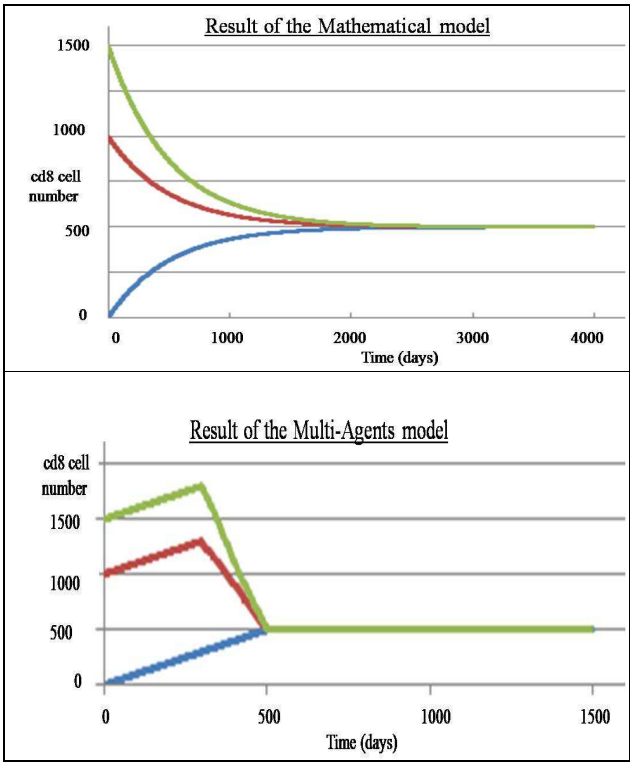
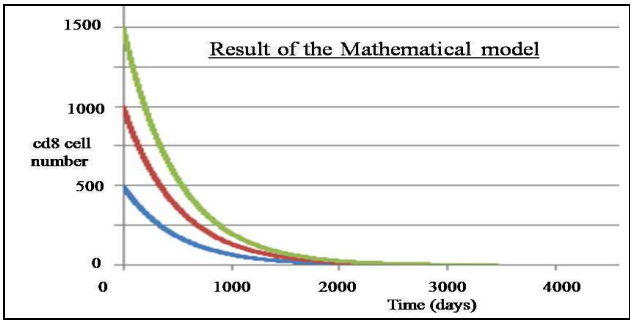


Figure 4. Evolution of the CD8 without infection.

We notice that the model Multi-agents converges more quickly than the mathematical model. The difference between both models appears also in the speed of extinction of an isolated population of CD8 cells, i.e., the rate of production is equal to zero (Fig. 5).



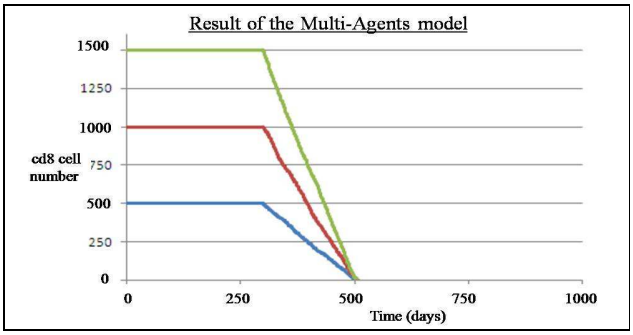


Figure 5. Extinction of the CD8.

The Multi-agents model shows that the population of the CD8 cells disappears immediately after 500 days (which is the lifespan of cells), and that happens independently of the initial number of the cells.

B. Evolution of the infection

In an environment, which represents 1 mm^3 of the blood, evolve four categories of cells: infected CD4, CD8, infected CD4 and the viruses HIV which interact between them by feigning the phenomenon of the infection.

In the presence of the infection, the CD8 cells play a defensive role. They exploit their cytotoxic capacity to eliminate the infected CD4 cells and consequently stop the production of the new viruses. The intervention of the CD8 cells is accompanied by a proliferation of these last where new CD8 cells are produced according to the numbers of the other cells (according to the mathematical model).

We notice that the two first phases of the process of the infection are recognizable on the various curves (Fig. 6).The phase of the primary infection is characterized by a growth of the viral population (initially little numerous) which invade CD4 cells (initially numerous). The infection of the healthy CD4 gives infected CD4 cells which are going to produce new viruses able to infect the others CD4. This growth persists until reach a maximal rate with which the reduced number of the population of the CD4 becomes a rare resource, consequently lot of viruses die without being able to infect CD4 and to produce infected CD4. In that case we notice a fall of the viral load and the number of the CD4 infected.

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

Figure 6 shows also the action of the CD8 cells. In the beginning, the production of the CD8 follows a natural production rate, but after the invasion of the viruses we notice that the number of the CD8 agents was increased considerably.

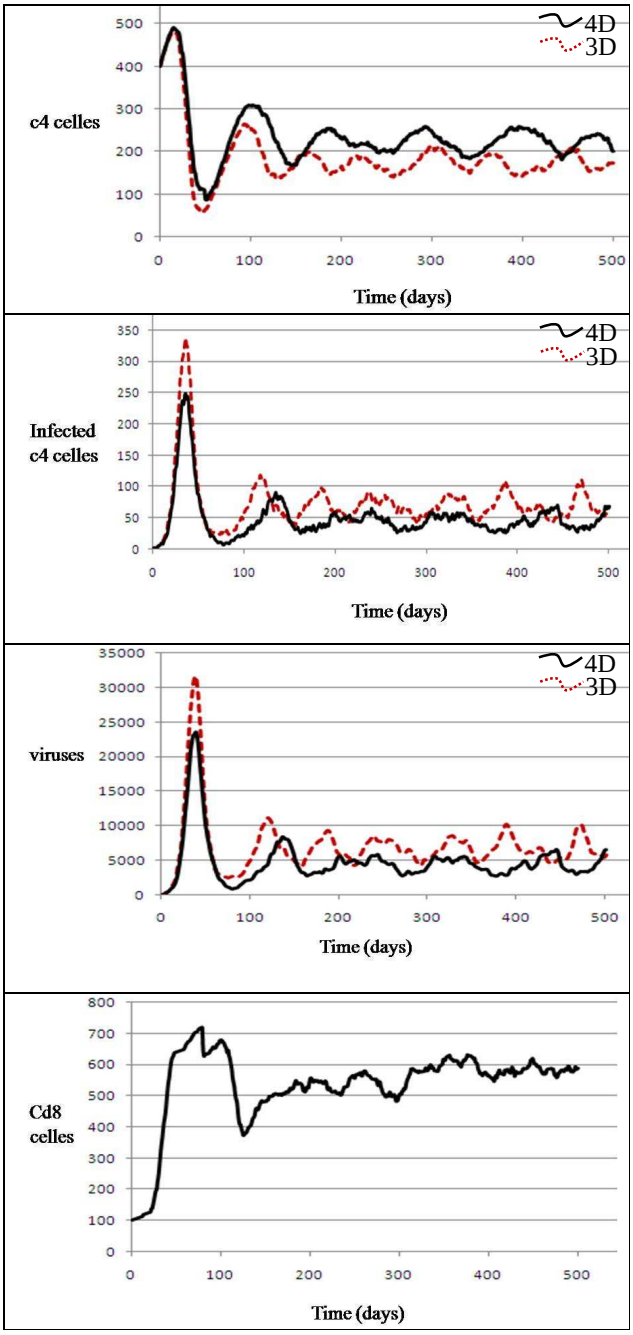


Figure 6. Results of the Multi-Agents model.

The strong increase in the CD8 agents returns to the proliferation of the latter. The action of the CD8 agents is double: destruction of the infected CD4 cells and the proliferation to reinforce the immunity against the infected CD4 cells (The proliferation of the CD8 reaches its maximum when the number of the infected CD4 is max i.e. during the phase of the primary infection).

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It is clear in the case of the 3D model (the dotted curve) that the number of the infected CD4 (consequently of the viruses) is more important than the one of the 4D model because there is no resistance from the system like the case of the model 4D.

Figure 7 shows the number of CD8 cells produced by proliferation during both phase of the infection.

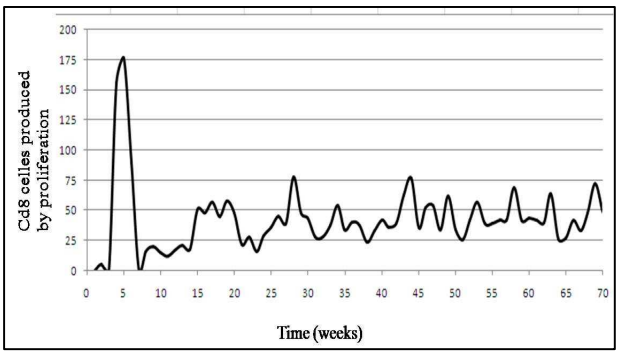

Figure 7. Cd8 proliferation.

If there were not infection of the viruses, the production of the CD8 remains constant. In the primary infection the number of the infected CD4 reached its maximum it is for that we notice the abrupt increase in the CD8 agents because of the proliferation (look at the curve of CD8).

During the asymptomatic phase, the number of the various cells (CD4, infected CD4 and virus) is stable thus we notice that the number of the CD8 agents becomes stable, more exactly; because the number of the CD8 cells agents produced by proliferation becomes more stable and weaker.

VI. CONCLUSION AND FUTURE WORKS

The population of the agents could reproduce the evolution of the biological phenomenon relating to the 4D model. This model enriched the 3D model by the behavior of the CD8 cells which influences the dynamics of the infection in accordance with the expected results from the biological phenomenon. We can see that during the asymptomatic phase the system maintains a rate of the CD4 cells more important than the one which is in the 3D model thanks to the effect of the CD8 cells. Our multi-agent model is extensible, in future work we will add the behavior of other cells involved in this bioprocess; because if we can build a complete multi-agents model for the phenomenon of the infection, we will be able to predict the evolution of the phenomenon and consequently to better direct the treatment.

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