Immune System Simulation through a Complex Adaptive System Model

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Abstract. Evolutionary algorithms and cellular automata are two computational approaches to model complex adaptive systems. Here is described an immune system simulator that uses a cellular automaton to model the physical environment along with an evolutionary genetic algorithm to attain adaptation and selection. Agent genetic coding comprised within the genotype is a set of rules which expresses behavior. Moreover, an agent includes a collection of operators which use the genetic code in order to interact with other agents and physical sites. We also depict the system's methodology as well as some of the obtained results.

***Keywords*: Artificial Immune Systems, Complex Adaptive Systems, Evolutionary Genetic Algorithms, Cellular Automata, Artificial Life.**

1 Introduction

Immune systems, ecological systems as well as many others, are difficult to control or describe using traditional computational methods. Two main difficulties are ensued when modeling such a system. The first problem arises from nonlinear interactions among system components. The second is issued when system's agents can evolve, or change their specification, over time. Systems with these properties are sometimes called Complex Adaptive Systems (CAS), and comprise the following [34]:

1. A collection of primitive components which will stand for the artificial entities, called 'agents.'
2. Interactions among agents and between agents and their environment.
3. Unanticipated global properties often result from the interactions.
4. Agents adapt their behavior to other agents and environmental constraints.
5. System behavior evolves over time, as a consequence of the previous properties.

Creating a model of a CAS is complex for several reasons. First, both nonlinearities and the changing behavior of the system restrain predictive mathematical models. Second, to model detailed simulations, computational problems exist, since expressing every detail is virtually impossible. For example, the vertebrate immune system can express, at a given time, over 10^7 receptors. Modeling such level of detail is computationally overwhelming. Therefore, in every large complicated system, precise computational modeling is virtually impossible, not only due to the former issue, but also because nonlinear system are highly dependent on small inaccuracies. To solve this problem, removing all the possible detail from the model, retaining only the essential interactions is a possibility. The goal is then to develop models whose behavior is sound with respect to the details of the interactions, and which produces the desired behavior classes. The major drawback with this approach is that such models will very seldom make precise quantitative predictions. Then, what are the expectations of a model that does not correspond directly to any real system? Patterns of behavior can be studied, such as how agents interact and cooperate under given

circumstances, which can be difficult to obtain in real systems. On the other hand, it is much easier to run what-if experiments than to conduct real system experiments. With a well designed model, theoretical reasoning can be built about evolution dynamics, such as agent dependencies and interactions.

In silico simulations are becoming powerful research tools through the definition of biological system models, namely immune system models, since a better understanding of important immunological phenomena is required to withhold the rising threat provoked by the offspring of new viruses and the contagious property of others, such as the HIV-I [17, 19].

This paper presents an Artificial Immune System (AIS) constructed using an hybrid approach that supports the evolving of an heterogeneous population of agents over an artificial environment. A genetic approach is used to model the agents while the underlying layer is supported by an object oriented cellular automaton. Genotypes are formed by tagged rules which express an agent's behavior, upon the interpretation of an operator. The immune responses comprised in the development of Acquired Immuno-Deficiency Syndrome (AIDS), provoked by HIV-I, are simulated using this AIS.

The structure of this paper is the following: in section 2 is presented some other work related with this system, namely some work on artificial life and on artificial immune systems. Section 3 discusses the methodology of the proposed system. Section 4 starts with an overview of the human immune system and the HIV-I virus. Follows the model used in the artificial immune system simulation. This section ends with the results obtained with this simulator. Finally, section 5 outlines some conclusions and future work.

2. Related Work

2.1 Cellular Automata

Although cellular automata (CA) have been used to model ecological systems, they offer a number of limitations when used *per se*.

The first comes from the fact that each CA site is static in space and can only change its state according to a set of local rules, not being able to stand for an autonomous agent. Another problem is related to spatial and temporal scaling. While CA models usually assume each place to be sized for one individual, this assumption proves inappropriate when modeling several ecological environments. Nevertheless, cellular automata are adequate to model some classes of environments. In [27] is presented a CA model for the study of competition between grass species. [26] addresses the effects of fire and dispersal on spatial patterns in forests. Various aspects related to the use of CA in the study of emergent behavior and Artificial Life in general, are addressed in [28].

When used along with other computational approaches, the cellular automata model proves best. An example is the Object-Oriented Cellular Automaton (OOCA) [23]. The OOCA uses a conventional CA as its lowest layer, where a set of agents, or devices, may interact with its sites, modifying or using their current state to decide what action to perform. Moreover, communication through message-passing mechanisms, resulting from object independence, allows actions to be directly performed over other devices. Thus, an OOCA model is easily extendible through the definition of new devices that possess different action rules. The modeling and simulation of biological systems which are prone to frequent changes, is one of the applications where the OOCA may be used to model the artificial environment. The Cellular Device Machine (CDM), presented in [5], is a system that comprises this approach. It includes a development environment that uses SLANG, a

dedicated object-based programming language, to express space and time relationships in large complex adaptive systems.

There are many examples of the use of the CA model that include genetic processing. In fact, all the systems described in the next subsection fall into this category.

2.2 Artificial Life

Genetic Algorithms (GA) are computational models of evolution which play a central role in many artificial life models. Fitness functions can be implicit, expressing the performance of an agent bounded by its environment, in the same way as natural selection. Moreover, genetic mechanisms can be easily modeled by way of genetic operators, and population dynamics can be simulated without complex mathematical models, as the set of simple local rules within a GA is usually sufficient. Consequently, it's not surprising that most evolving Artificial Life applications use the GA as a basis [33]. Several examples are described next.

A model for an ecological system simulation is proposed in Echo [30], [31], [32], [34]. In this system, a population of agents inhabits an heterogeneous lattice, where each site can be shared. The lattice serves also as a resources repository of different types. Agents can interact through mating, trading and fighting. A set of rules define the interaction among agents. Likewise, a set of attributes, corresponding to its external "appearance", is encoded in the string that forms its genotype. The fitness function is endogenous, and reproduction is made by cloning, with low mutation probability. Genetic material is exchanged between agents by mating.

In [2] is addressed the simulation of bean and weevil population, emphasizing the role of contest and scramble competitions on its evolution. The system uses a diploid GA, coding all life parameters in a bit string.

The evolution of a size-structured predator-prey community is studied in [24]. Organisms are grouped accordingly to their size: those of the smallest class are autotrophs; all the others are heterotrophs which can kill organisms of smaller classes. The attributes of an organism are coded on a bit string, and their surrounding environment consists of a lattice through which the organisms move in random directions depending on the organism size.

Game theory is used to model evolution and interaction between species in food webs that result from explicit resource flow [25]. The fitness of a species - which constitutes its rate of reproduction - is proportional to the amount of accumulated energy. The latter is distributed among the organisms taking into account their score in the game. The main part of a genome is the strategy gene which defines an organism's behavior. Genomes are subject to three kinds of mutation: single bit mutation, gene duplication and split mutation. While gene duplication increases agent memory, split mutation performs the opposite by dividing the genome into two parts and randomly choosing one of them to be kept.

Several other Artificial Life articles focus on other important issues, such as the impact of environmental topologies in artificial ecological systems. Topology impact in various kinds of communities formed by two interactive species is studied in [1]. Among the conclusions, are the role of an homogenous topology: fully connected graphs which promote rapid growth and higher population levels than local and random-graph topologies. It is suggested that while local topologies, such as the nearest neighbor, offer special interaction restrictions, homogeneous ones offer no barrier for the individuals inhabiting the same place.

A survey on the role of Genetic Algorithms in Artificial Life can be found in [33].

2.3 Artificial Immune Systems

Some important work is being developed at the University of California at San Diego and at Santa-Fe Institute on Artificial Immune System models, including HIV-I simulation.

The previously referred CDM is the platform of research at the University of California at San Diego. In [4], is presented a Cellular-Device Machine simulation of the HIV infection in an artificial immune system, where the state machines which depict model behavior are described. A detailed analysis of the results is presented as concentration progresses for both immune system cell agents as well as for soluble substances. When compared to the data obtained *in vivo*, the results were surprisingly accurate. Observed responses include: systemic patterns, like the predominance of the macrophage reservoir; increased IL-2 responsiveness on CD4 T cells; higher productions of both IL-1 and γ-IFN when matched with IL-2 and IL-5.

The hu-SCID (Severe Condition Immuno Deficiency) mouse lymph node simulation is publicly available at [23], and also uses the CDM. Its set of devices comprises T lymphocytes, macrophages, and stoma cells of the lymphatic tissue. The SCID mouse presents initial immuno-deficiency and xenografts of human cells are used to complement the immune system. It is observed the lymph node's response to virus infection, and results have already been obtained for HIV-I. Some of them helped to conclude about the role of macrophage-tropic HIV-I in AIDS development [7].

Another Artificial Immune System is being developed at the Santa-Fe Institute. It uses a set of differential equations whose parameters are adapted by a neural network. Like the human nervous system, the immune system performs pattern recognition tasks, where antigen presentation to the neural net induces system learning. Some issues of this work are presented in [29].

3. Methodology

Our system addresses two different questions: how to model artificial independent individuals; and how to set up an artificial environment, able to provide feedback and support interaction.

Individuals are modeled by way of self-ruling devices, called agents, which can interact with the system as well as with other agents. Comprised within each, lies every mechanism required to express its internal behavior and to respond to system feedback. Since each agent is an independent and closed device, heterogeneous agent populations are directly considered. Communication can be either the result of direct agent interaction, or indirect, using the underlying environment as platform. Each entity has a particular set of rules which determines its external interaction mechanisms, or behavior. These rules are encoded within each gene of the agent's chromosome. Hence, a gene is a partial state controller, where if-then or other type of rules may specify the behavior. Each gene can keep a different format rule, along with other data, such as the conditions under which the rule is to be applied. Therefore, the agent's genotype is the fusion of all the current genes within the chromosome.

Behavior relies in a set of operators which decode specific genetic information and act accordingly. This operators use no explicit fitness function, instead they use environment and genetic information to guide the agent. Thus, global behavior is obtained through each local operator's evaluation of the genetic rules comprised within each agent. Moreover, each agent can present the environment and other agents with a set of external features, which may be also encoded in the genetic code. On the other hand, the number of genes and operators is not fixed, allowing dynamics during the agent's evolution. With this approach, each agent comes as an autonomous device, where its behavior is given through a function of the current set of rules, environment feedback and external information presented in other agents. Furthermore, genetic rules are mapped into a variable length chromosome, which can hold an arbitrary number of autonomous genes at each instant. This proves to be an attractive feature, especially in the modeling of immune systems where genetic code modification exists.

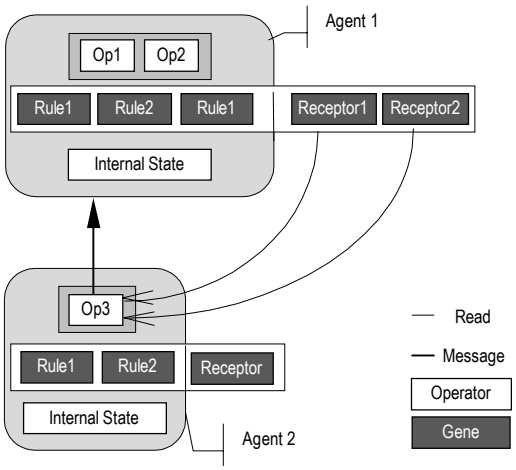


Fig. 1. Agent internal structure and inter-agent relationships. Particular genes, included in the agent, may be visible to the surrounding environment, acting as receptors. Operators can interfere with other agents using message-passing mechanisms, while receptors may serve as input devices.

The agent population is distributed over a set of sites comprised in the lattice, which, along with the corresponding spatial relationships, can be expressed through an object-oriented cellular automaton. This allows a detachment between each physical location and the lattice that comprises them. Moreover, agents and environment will also become separated. Since each lattice site can be different from all others, it enables the construction of heterogeneous site worlds.

A further extension to the usual OOCA container location allows each site to be active rather than to simply hold data. This is accomplished by assigning a local processing function to each site, which is used to decide what local action to take upon its current information, providing a measure of locality within each site. Many agents can cohabit at the same site, and, since each location has a degree of activity, it can interact with the devices it currently comprises. This allows a twofold mechanism between devices and the artificial environment, providing the means to model environmental hazards or other features.

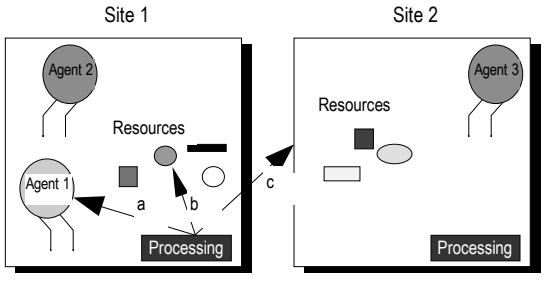


Fig. 2. Each site is self-contained and can hold several agents simultaneously. The measure of locality is provided through a local processor which can interact with the agents comprised within (a); interact with the local resources (b); and interact with other independent sites (c).

The outcome of binding both mechanisms above described resulted in an hybrid architecture which has, on the one hand, the advantages of outlining each entity through a genetic approach, and on the other, the usefulness of having an autonomous layer controlling

and providing mechanisms to simulate artificial world interactions. The genetic approach allows natural selection to be achieved through an endogenous fitness mechanism, emerging from the actions and interactions with the system as a whole.

Artificial life simulations can be accomplished with this methodology through the definition of rules which depict behavior. Likewise, the creation of an heterogeneous artificial world is straightforward, for each site's local 'behavior' can be expressed through the outlining of a local response function.

The cellular automaton layer uses a synchronous update policy to express the simultaneous transitions that would exist in a biological environment if observed as a discrete system.

Every cycle the population is prompted to interact with the system. A notification is then sent to every agent, which has the external result of mapping the genotype into the phenotype through its set of operators. First, recall that every entity is self-contained and each chromosome may vary in the number and type of genes. Therefore, behavior results as function of the device's operators over the required genetic code included in the entity's chromosome. With this approach, every entity can hold several operators along with variable-length chromosomes, as formerly stated.

The sequence of events in each simulation cycle consists of the following:

1. Every agent located at each site is prompted to evaluate the current environment along with the visible features of other agents. This will update the agent's set of triggering conditions.
2. Every operator executes the rules contained in the corresponding genes, using the current conditions' state, set in the previous step. In this way, agent-agent and agent-environment interactions take place and external features are presented.
3. The environment interacts with the agents upon site local data and specific rules.
4. Environment-environment interaction. Site resources are modified upon local rules.
5. 'Dead' agents are removed from the lattice.

As an example, suppose the simulation of a system where two different agent classes were comprised (Fig. 3). Each entity moves conformably with a specific pattern. Crossover can be performed by entities of different sexes, and is followed by a gene mutation in the offspring. The artificial world is composed of two types of locations: L1, where substances spread to same class sites where its amount is scarcer; in L2 locations substances do not spread but dissolve locally at a certain rate.

To simulate this artificial world one needs to define two different features: first, define the behavior of each one of the agents. This is accomplished through the definition of the genetic rules and operators which hold its behavior. An agent is then able to autonomously perform the task subdued to its set of rules; second, define the underlying environment. This is done by creating the local rules for each independent site.

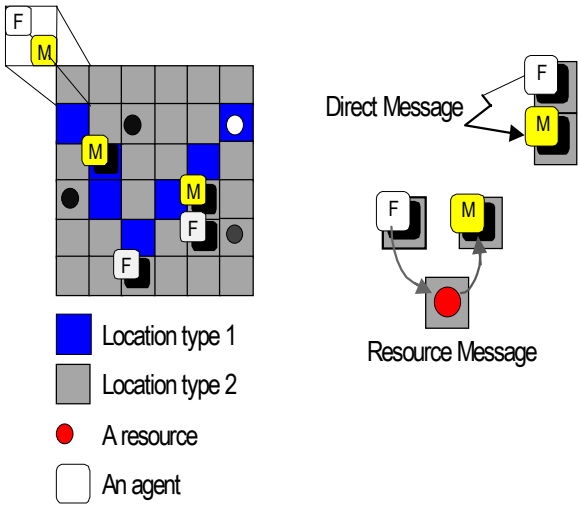


Fig. 3. An example of an artificial world. Each entity's chromosome holds the current behavior rules. Interaction among agents can take place directly using message-passing mechanisms, though the cellular automata's locations enable indirect interaction through resources. Any resource or agent within a site is bound to its local behavior rules, enabling resource local handling and environment-agent communication.

4. The Artificial Immune System

4.1 Human Immunology

The human body is repeatedly attacked by several infectious intruders present in the surrounding environment. Although these intruders can cause disease and eventually lead to death, just a few engender injury to the human body, since the immune system is able to deal with numerous microorganisms. The human immune system consists of a series of layers, from the most external one, the skin, to the internal immune system. The latter comprises a large group of cells whose primary function is to eliminate infectious agents and to minimize the damage they might cause.

An immune system response involves, in the first place, recognizing a pathogen and secondly triggering a reaction in order to eliminate it. These reactions or immune responses fall into two categories: innate (or non-adaptive) and adaptive responses. The innate responses can successfully destroy many pathogens on first encounter using substances present in the blood stream such as complement. However, this is not enough to provide protection against all infections, as the rapid evolving of the pathogenic agents provides mechanisms able to evade the innate immune defense. To counteract, most vertebrates including man, are able to respond to any foreign substance even if it has never been faced before. The adaptive immune system involves two main features: the specificity, leading to a highly precise response for a particular pathogen; and the memory, causing a response improvement when dealing with the same infectious agent once again.

After a pathogenic agent successfully breaks through the external defense layers, peptides called antigens make possible its recognition and later eradication. Each immune system cell is able to recognize a single specific antigen, and only the system as a whole can

detect thousands of it. Yet, upon antigen recognition, a rapid proliferation of these cells is induced to render an adequate immune response, the so called clonal selection.

Immune responses are produced by leukocytes, of which there are several types. One group is the phagocyte cells, such as the macrophages. These cells bind to the foreign substances, internalize and then destroy them. Since they use non-specific antigen recognition they all produce innate responses and act as the first line of defense against infectious agents. Another group of leukocyte cells are the lymphocytes. Broadly, they fall into two categories: the T cells and the B cells.

The B cells, after recognizing a particular antigen, rapidly divide and differentiate into plasma cells, which can produce large amount of specific antibody. This substance binds to the target antigen that initially made the B cells active. Other B cells remain in a so called memory state for they retain immunological memory for a particular antigen. Memory cells provide the means for a lasting immunity to a pathogen, and the basis for vaccine development. Hence, the aim of vaccination is to modify a specific pathogen in such a way that they become innocuous without losing their antigen presentation. This is possible because antibodies and T cells recognize antigen and not the pathogenic organism as a whole. In other words, vaccination is a method that increases the immunological response against a pathogenic substance, by taking full advantage of the specificity and memory of the adaptive immune system.

The second lymphocyte group, the T cells, are involved in a larger set of activities. The T cells bearing the CD4 marker, also named T helpers, further influence the response of T and B cells and induce the immune system's cytotoxic function. The CD8 T lymphocytes, also called T killer lymphocytes, eliminate cells that display antigen on their surface. This is accomplished by releasing cytotoxic substances that will rupture the cell's cytoplasm leading to its destruction.

When a pathogenic substance is internalized in a cell, it releases non-self peptides which are presented through specific proteins called the major histocompatibility complex (MHC). These molecules are divided into two classes, named MHC-I and MHC-II, being the former found in almost all types of the body cells. However, the latter appears only in cells related with the immune response. It is the presence of foreign peptides in the MHC that tells the immune system whether a cell is infected, since in a healthy cell all the peptides come from self proteins. The foreign peptides in this way presented can be then recognized by T cells, namely CD8 cells.

The two classes of MHC molecules present peptides that arise from different places within the cell. Class I molecules bind and present proteins resulting from the continuous peptide processing and renewal that takes place inside a cell. These proteins are then carried to the cell's surface, where they can be later recognized by CD8 cells. If the peptide presented is non-self, say from a virus infection, the CD8 cell releases cytotoxic elements that will destroy the host cell. This response is the only effective way to prevent the creation of more viruses by the infected cells and hence avoid the infection's outspread.

On the other hand, MHC class II have the ability to seize any peptides they find inside the cell and then deliver it to the cell's surface, unlike class I molecules, which are limited to the non-nuclear compartment and can only bind to a specific peptide after a molecular reorganization. The peptide presented can only be recognized by T cells which have the CD4 marker. Therefore, the identification of an infected cell through the MHC-II complex does not lead to the cell annihilation, rather, CD4 cells activate those which have displayed the foreign peptide. For example, a CD4 cell can stimulate a macrophage to destroy the pathogenic elements contained in its structure. Also, the helper T cells after identifying a non-self peptide on the cell's surface, produce cytokines, namely interleukins, involved in cell differentiation and division.

A large diversity of molecules is present at the onset and throughout the development of immune responses, including complement, a key substance in the non-adaptive response, and other soluble mediators of immunity such as the cytokines and the antibody.

The cytokines hold a wide variety of molecules which are bound in cell signaling and triggering during immune responses. Although there is high diversity in this group of molecules, they fall into a number of categories.

Interferons (IFN) are proteins that are characterized as strong immune regulators and growth factors. They fall into three classes: IFN_{α}, the largest variant, produced by leukocytes; IFN_{β} made by fibroblast in response to viruses or nucleic acids and IFN_{γ}. IFN is produced by activated T cells as the outcome of immune activation. Therefore, this substance leads to an increase of the antigen presenting cell (APC) function, and will further activate other T cells and macrophages as well. IFN_{γ} is responsible for regulating the APC function of many cell types, and an excessive production of this substance is a factor of the auto-immunity induction [35].

Interleukins are in majority molecules made by leukocytes which act on leukocytes, mainly T and B cells, represented by the abbreviations IL-1 through IL-11.

IL-1 or catabolin, is made by many cells, including B cells, but in its majority is produced by macrophages. It stimulates T and B cells providing a means to perform immuno-regulation, and induces inflammatory responses and fever. Virtually every cell in the human body can respond to this molecule.

Another interleukin, IL-2, previously known as T cell growth factor, is produced by T cells, mostly by CD4 cells. Its range of response is limited to T cells where it acts as a powerful growth factor and activator (e.g. enabling the T cells to release IFN_{γ}). It also acts on B cells, inducing growth and differentiation, and further activates macrophages.

IL-6, also known as B cell differentiation factor, is produced by T and B cells, macrophages and other cells. It induces B cell differentiation, which will cause antibody-forming cells (AFCs) to be produced.

Colony-stimulating factors (CSF) are involved in the division and differentiation of stem cells. The balance of these cells determines the proportions of the different cell types to be produced. Tumor necrosis factors (TNF) and transforming growth factors (TGF) are particularly important in mediating inflammation and cytotoxic reactions.

The interaction between T cells and the antigen-presenting cells (APCs) is the most important issue in immunological response. Only if CD4 cells are in sufficient number and are successfully triggered, the activation and subsequent response of B cells will follow. Otherwise no immunological response will take place.

Both T and B cells are activated upon a successful bind to an antigen. B cells can bind to free antigen but generally need T cell's help to become activated, whereas T cells can only bind to antigen presented in MHC molecules. After the interaction with the cell's specific antigen, a number of internal biochemical reactions will modify the cell's DNA. At the same time, the cell develops the ability to respond to specific cytokines, such as IL-2, by producing receptors on its surface. The response to those cytokines will cause cell proliferation and maturation.

Clonal selection is an aftermath of the offspring of specific cells, able to recognize a specific antigen. In this procedure, called primary response, some cells develop into effectors or activated cells while some others become memory cells. The second type of cells, the memory cells, will home to certain areas of the lymphoid tissues where they remain ready to respond to the same antigen if it comes across again – the secondary response. Therefore, the secondary response against a specific type of pathogen will prove to be more effective as it develops an immune response more rapidly.

4.2 The HIV Virus

Viruses are the smallest known organisms, and yet they constitute one of the greatest threats to human health. However, they hold a minimal design: a protein capsule, holding RNA or DNA, where the genetic code for the virus survival and offspring remains. Thus, the

success of a virus depends on infecting and then modifying a cell's genetic code in order to produce more viruses.

Certain virus, such as the HIV-I, can have a peculiar property: it can take both active and latent forms. During the active phase, the virus interferes with the cell's normal metabolism, causing the symptoms associated with the disease. When in the latent phase, the virus remains in quiescent state in the infected host cell, although the host is a symptom-free carrier of the disease. The latter state can endure for several years.

The Human Immunodeficiency Virus (HIV-I), also known as Human T-Lymphotropic Virus-III (HTLV-III), usually enters the serum or blood stream within a foreign macrophage or helper T cell. These foreign cells are correctly recognized as non-self particles and are encapsulated by the body macrophages. The virus remains unaffected inside the carrier cell until it pierces the host cell's membrane and waits for the antigen to be presented on the macrophage surface. When the host's helper cell binds to the antigen, the virus will infect it. This cell-type specific attack is unique among retrovirus.

The HIV-I virus may also stay inside the original macrophage, where it may reproduce and bud into vacuoles which are kept within the macrophage's cell membrane. In this manner, the virus will not be detected or recognized by the body defense mechanisms as it is still encapsulated within a body cell. This allows amplification of the virus without the body becoming aware of its presence.

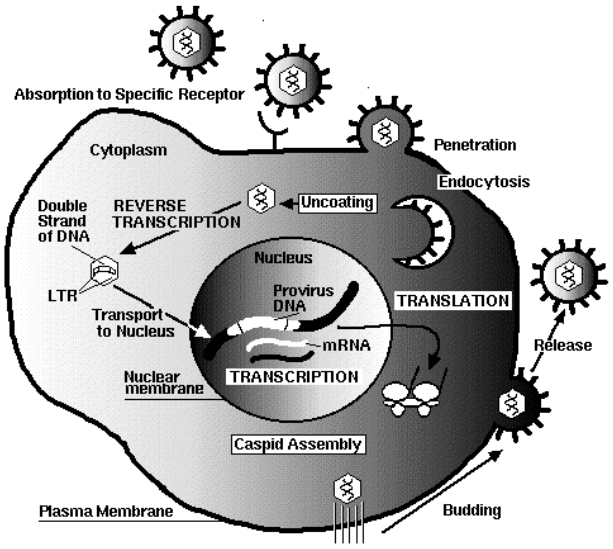


Fig. 4. HIV-I retrovirus replication cycle

Usually, IL-1 is released by a macrophage that has seized a non-self particle. An infected macrophage demonstrates a reduction in chemotaxis and releases a substance that disables the activation message from getting to T cells, preventing the immune response cascade. The infected macrophage or helper cell will eventually home to a lymph node. Here the virus will proliferate, transfer and infect other macrophages and helper cells, and eventually collapse the lymph node, decreasing the total circulating lymphocytes.

The normal infection cycle involves the cycling through the macrophage, positioning itself on the macrophage surface and infecting the helper cell. The last is entered through endocytosis and injected with the HIV provirus. The viral RNA is then converted by reverse transcription into DNA which then inserts itself into the original DNA of the host cell. Here it may remain latent for several years, or become active.

The HIV attack is specific to the CD4 and related inducer cells. These cells normally compound 60-80% of the circulating T cells. After a successful infection, this number can be reduced to such a degree that it is impossible to detect their presence. As the active virus

multiplies, it pierces the membrane of the CD4 cells, killing them. Infected cells also secrete a toxin which is fatal to other non-infected CD4 cells, but which does not kill those already infected.

The HIV virus not only reduces the cell population, but also modifies their function. Each CD4 cell usually produces about 1.000 clones when properly stimulated. An infected cell can produce as about 10. This loss of reproductive ability eventually collapses the helper T cell population except for the few HIV infected cells, following the disruption of the immune system.

For several reasons the HIV virus is especially complex for the body to attack. First, the virus undergoes rapid enveloping protein mutations. This means that the antibodies produced to restrain the recognized antigen will try to bind to a virus that no longer exists. For the same reason, multiple strains of the virus will coexist within the body, each carrying a different protein coat, turning the virus immune to the original antibody. Secondly, the HIV virus will incorporate into its protein envelope, part of the host cell membrane as it ruptures and kills its host. This membrane makes it nearly impossible for the body defenses to recognize it as non-self. On the other hand, the virus blocks the binding of molecules to MHC-II in helper T cells. The MHC-II will not bind, immuno-reactions will decline and the level of IL-2 will fall, decreasing the global immune response level. This means that the helper T cells are not going to be activated against an antigen, which in turn stops the T cell immune system coordinator response. No helper, killer or B cell multiplication and no antibody production. The damage done to the immune system as a whole is permanent and irreversible. The effect of all this devastation removes all immune system protection from the body. Hence, any pathogenic invasions normally present within the body are no longer held in check. The body would be wide open to any external attack.

It should be pointed out that in all cases the immune system will mount an immune system response. It usually even goes so far as to produce effective antibodies against the virus. Unfortunately, when the response comes it is already too late.

4.3 AIS Simulation Model

Artificial immune system simulations aim two broad areas: hypothesis generation and experiment prototyping. Since every complex system comprises a large parameter space and a variable set of emergent behaviors, a computer simulation provides guidance in order to identify the system's dynamics from the basic immunologic data. Modeling hypothesis in disease processes and therapeutic intervention is a natural outcome. On the other hand, laboratory experiments are not able to uphold the parameter settings necessary to fully resolve the problem considered. Therefore, in parallel with the *in vivo* investigation, *in silico* experiments can be used to bound the parameters that will most likely yield interesting laboratory resultsband to classify the global behaviors found in the whole parameter domain.

To simulate the immune system, specific agents and an adequate underlying environment were first identified and later modeled. Several behavior rules were then tested in order to obtain a set of results which related to those from a real system.

The artificial immune system agents here considered may be separated into two main classes. The first one contains the immune system cells, namely four types of leukocytes: B lymphocytes, CD4 T lymphocytes, CD8 T lymphocytes and macrophages. The other class is a set of pathogenic agents, specifically the HIV-I and two other theoretical viruses, RB and V*, whose function is to present the system with a series of situations, allowing the study of different immune system responses. The RB virus simply releases specific antigen, leaving the immune system cells unscathed, while V* infects TH cells and remains latent for a random period. When activated it kills its host cell.

A subset of immune system soluble mediators is included in this model, comprehending Interleukin-1, Interleukin-2, Interleukin-6, γ-Interferon and cytotoxic agents

produced by T killer cells. Antibody and antigen is produced or secreted accordingly to the pathogen's type.

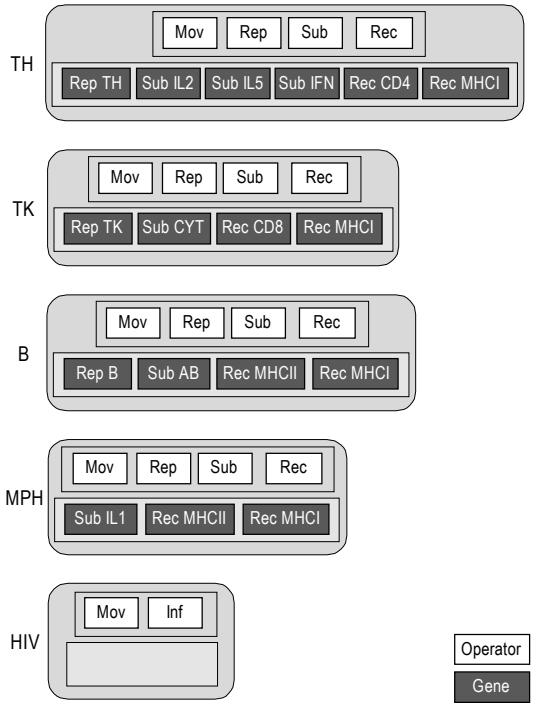


Fig. 5. Initial genotypes and operator sets of the AIS agents

Agent operators are guided by their host's genotype. To model the artificial immune system, several types of genes were considered, each one including a specific part of genetic code:

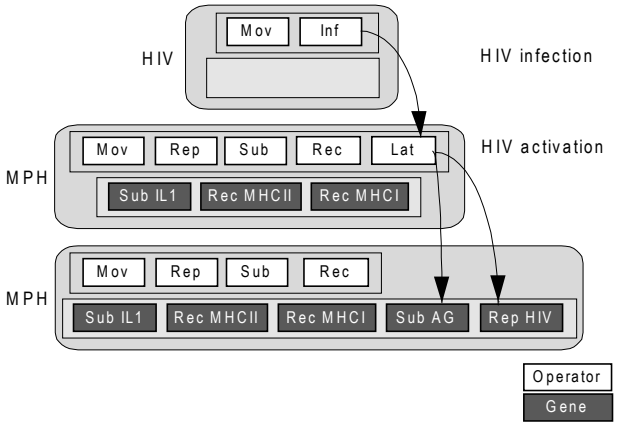


Fig. 6. HIV infection mechanism. Virus infection is accomplished through the injection in the host cell of a pathogenic operator, which remains in latent state. Following activation, the operator modifies the genetic data of the cell using the virus' essential behavior rules. The cell's phenotype, which is the interpretation of the genetic data using the current operator set, will then include the virus' behavior. Throughout this process, the cell remains unaware of the pathogenic agent.

1. Reproduction or division genes. Contain the condition code, triggering probability and data about the new cell.
2. Substance secretion genes. Keep the condition code along with the release probability for a specific soluble mediator.
3. Receptor presentation genes. Contain the condition code and presentation factor of a specific receptor.

The agent's operators verify the state of the condition's codes in the genes they use to perform their specific action. Healthy cells of the immune system start with a set of four operators:

1. Reproduction operator. This operator creates new agents using the information within the Reproduction genes.
2. Substance secretion operator. This operator releases the substances expressed in the Substance genes.
3. Receptor operator. Presents proteins expressed in the Receptor genes to the environment
4. Movement operator. Models cell movement, but as every agent rely on fluid movements to perform this action, this operator needs no director genetic code.

Each pathogenic agent holds a specific Infection operator, which may append an extra operator to the cell when a virus agent infects a cell. In the specific case of the HIV-I, this operator, the Latent operator, remains idle until virus activation conditions apply. This model considers that HIV-I is activated upon an immune response of the host cell. Once activated, this operator modifies the host cell's genotype. This is attained by adding two extra rules: HIV-I antigen secretion and HIV-I virion reproduction. The cell behavior will then comprise the virus' rules, every time the genotype is interpreted. Additionally, the MHC-I receptor condition is set, once the foreign genetic material is detected. Initial operators and genotypes for every agent are shown in Fig. 5. In Figure 8 is the resultant behavior for each modeled agent. Finally, the model for HIV-I infection mechanisms is depicted in Fig. 6.

The artificial environment is modeled using a toroidal manifold lattice, since the environments here considered are closed. The soluble mediators are spread using a concentration ratio basis, flowing to where they are less clustered. Substance dissolution results from decreasing each one a fixed value each simulation cycle.

The computational application developed to support the artificial immune system simulator comprehends a set of features:

- User-defined graphics can be constructed from all the substances and agents comprised in the simulation. Scale adjustment is possible.
- Graphical data file output complies with CSV (Comma Separated Values) format, which can be used in common spreadsheets.
- Simulation parameters can be adjusted, enabling dynamic settings. This includes environment settings and agent parameters.
- System configuration and parameter settings may be stored and later retrieved.
- A view of the environment is available where the agents comprised in the system can be observed. Moreover, a graphical notation is used in order to follow the agents' status, enabling the trace of agent's distribution patterns.
- Substances and agents in any state can be added to the system through a syringe tool.
- Events related with user interference are traced into a log, which can be stored, and later be used to identify specific system responses in previously obtained graphics.
- Simulation temporal control, step and breakpoint conditions can be controlled by the user.

5. Results

Facing the simulator with a set of typical situations, a strong resemblance was found between the obtained results and those from a real immune systems, validated through several sources [3, 4, 7, 23, 35].

The system was firstly submitted to a series of tests in order to verify the role of the modeled soluble mediators in the regulation of immune activities. The first test aimed Interleukin-1 and Interleukin-5, and the obtained results are in Fig. 7. In point *A*, T helper cells were introduced in an otherwise empty system. The system was challenged with antigen upon the addition of RB virus, in instant *B*. No immune response was observed, for T helper cells are not able to recognize antigen in free form, only MHC-II/antigen pairs, thus requiring the help of antigen presenting cells. APC cells, namely B cells, were introduced in instant *C*. T helper response was still unobserved, since IL-1 is required to attain a successful activation, and is produced by macrophages, which were not considered in this system. On the other hand, B cells only react in presence of IL-5, which in turn is secreted by activated T CD4 cells. To overcome this deadlock, IL-1 was injected in instant *D*, which led to the chain of the immune response. As an aftermath, the pathogenic agents were successfully eliminated.

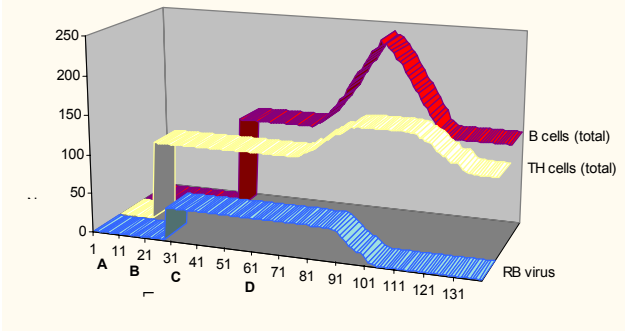


Fig. 7. IL-1and IL-5 as regulators of the immune system. IL-1 was presented in instant *D*, resulting in IL-5 production. A typical immune response followed. The importance of cell cooperation and immune mediators was asserted.

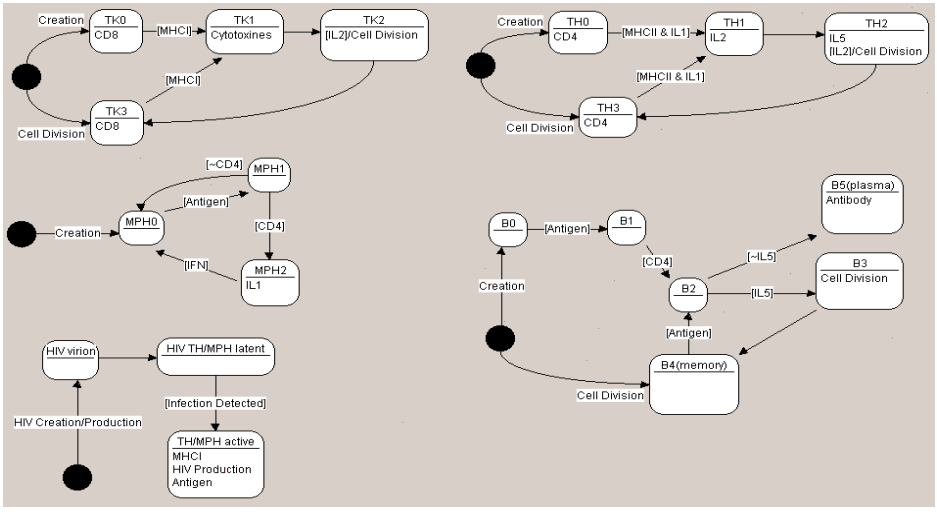
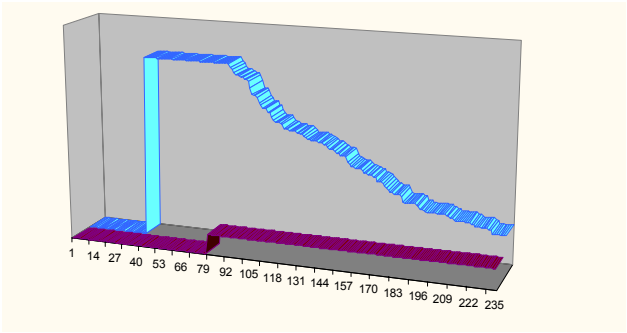


Fig. 8. AIS rule induced state transition diagrams, expressing device behavior. In *a, b, c,* and *d* is shown behavior for T Killer, T helper cells, Macrophage and B cells. In *e* is shown HIV activity in the immune system.

The second experiment evaluated the role of IL-2, and was parted in two. In the first case-study (Fig. 9), the system comprehended no cells at the onset. In *A*, a number of HIV infected macrophages were added. The addition of T killer cells followed in *B*, which led to a progressive destruction of the infected macrophage population. The second part of the test is depicted in Fig. 10, where the former process was followed, apart of Interleukin-2 being injected in instant *C*. IL-2 acted as a growth factor, increasing the number of T CD8 cells. The outcome: a more rapid destruction of infected macrophages.



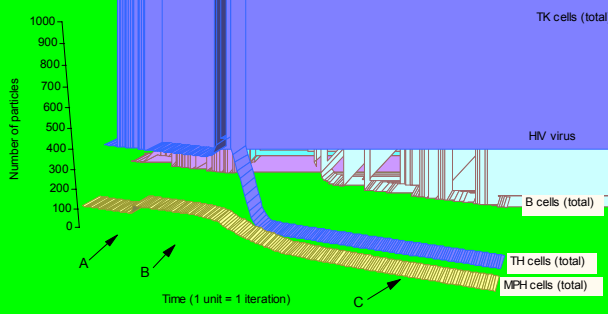


Fig. 12. HIV-I infection, T CD4 and macrophage depletion. Firstly, the healthy system received a number of HIV infected macrophages (A). Later, the introduction of RB antigen caused an immune reaction, increasing the number of B and T helper cells. However, the outcome of the immune response was the activation of the HIV virus, which led to a systematic production of HIV virions on the part of the infected cells, spreading the infection. As more and more T helpers and macrophages became infected, T killer cells took their toll from them, leading to helper and macrophage reduction, resulting in AIDS. In C the system was again presented with RB virus antigen. This time it yielded no response.

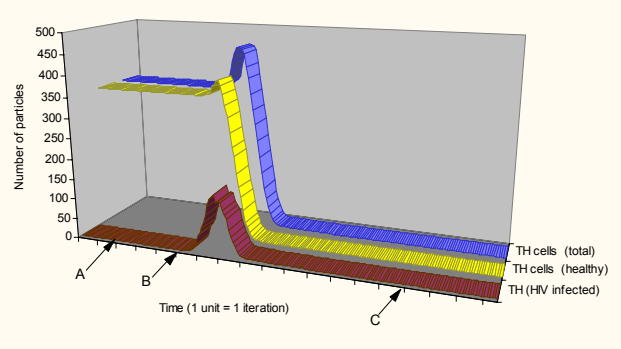


Fig. 13. T helper depletion is the main cause of AIDS during an HIV infection. The initial augment of T helpers can be clearly seen in moment B, as can be also seen the effect of HIV activation and production by the increase of infected helpers. A rapid decrease follows, eliminating the capacity of the immune system to respond to further infections.

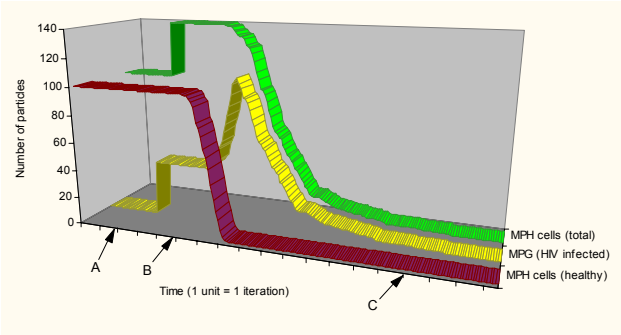


Fig. 14. At the onset, no macrophages were infected with HIV-I. The introduction of HIV infected macrophages saw no hostile reaction, as the HIV virus subsisted in latent state inside the infected cells, and thus TD0hus Tm.16tuq

The obtained response is shown in Fig. 15: the resultant T helper immune response and V* production are almost periodic and their pattern resembles the one found in predator-prey communities.

After V* infection and later activation, its production is enabled and the infection spreads. This comes as consequence of TH cell response, since an increase in helper cell population will expand the V* number, resulting on a major infection in the TH compartment. On the other hand, V* production also leads to a decrease in TH population, which in turn causes a progressive diminishing in the V* population. However, the V* virus will continue to activate the immune system cells, including the T helper cells, leading to another cycle.

The system is also used in a more serious simulation of the immune system [37], where the behavior and type of immune responses currently believed to be the result of cross regulation of $CD4^+$ T lymphocyte populations are investigated. Many debates have arisen concerning the way the immune system is able to provide an immune response and tolerate self simultaneously. Classical theories try to explain these phenomena through the specificity of T cell receptors. Nevertheless, observations showed us that the specificity of the immune system cells can be quite degenerated, providing a different scope on the understanding of the immune system's balance.

We proposed and implemented in this simulation system a computational model for the dynamics of Th_1 and Th_2 $CD4^+$ T lymphocyte sub-populations. The aim is the study of diversity and multiple responses. Using this model we are able to identify some experimental observations which are poorly understood. Some of the results showed us that the immune system's balance can be related to a measure of locality, helping to explain the paradigm of concomitant responses and tolerance. The model enabled both TCR and MHC/peptide diversity considering different matching coefficients with the same antigen, which makes it suitable for simulations concerning *in vitro* and *in vivo* test protocols. Moreover, the ontogeny and the dynamics of Th lymphocytes appear to be one of the major regulatory mechanisms that upholds the tolerance and rejection of the immune system. We note that the establishment and maintenance of local equilibrium states, a process in which cytokines appear to have a decisive role, may help to understand one of the many important phenomena in the immune system. The proposed model gives interesting clues on the learning process the immune system is submitted during its ontogeny and on how a population that presents a very degenerated specificity can recognize both self and allogeneic antigen. These results somewhat contradict the more orthodox theories which put exclusive specificity as the main factor for immune regulation and immunity.

6. Conclusions and Future Directions

Summarizing, the system presents an hybrid architecture that allows the modeling of systems involving multiple heterogeneous agents, physically distributed on a lattice made up of dissimilar elements. Agents are autonomous devices, containing a chromosome whose length may dynamically change, and a set of operators that express behavior based on a set of rules encapsulated throughout the gene structure. A collection of operators interpret the genetic rules and may also use external information, whether seized from external information presented by the environment or by other agents.

Interaction is not limited to the usual agent-agent and agent-environment, since each environment site is an active entity. Thereupon, a site can also interact with the agents comprised within it. In addition, environment-environment interaction is made possible since the site lattice is an active network, where each location has a local processing engine. Thus, the system architecture consists of three main layers, with the physical lattice forming the

lowest level. At the second level, the network of active sites keeps local data and uses the processing engine either to interact with the data or to modify it. Finally, at the highest level, is the multiple agent population.

Artificial immune system simulators aim the domain of hypothesis generation and experiment prototyping. This class of systems can help to design rational therapeutic intervention as well as understanding the process of disease. Moreover, the system's large parameter set can be constructed upon what-if hypothesis, otherwise difficult to attain in laboratory. The resulting data, obtained from *in silico* simulations, can support clinical trials and diagnosis and further bound *in vivo* laboratory tests to a set of experiments which will probably lead to attractive outcomes.

The system's complex parameters may be optimized through a Evolutionary Genetic Algorithm, whose fitness function equates both the current output and the data from real immune systems. The resulting data the parameter chromosome holds, can be used in a twofold manner. On the one hand, it comprehends the settings for a suitable model, according to the given data. On the other, the resulting parameters can be used to formulate theoretical assumptions on how the settings induce the system's behavior.

Besides the HIV-I simulation, other viruses, can be simulated with respect to the class of macroscopic responses here modeled. To attain this task, one first requires to identify and outline the pathogenic agent's behavior, and then construct a set of rules which model the virus.

The results showed how the complex and emergent behavior can be the result of the interactions among immune system agents. It was asserted that the model possesses antigen memory, one of the main features of a real immune system. The system was also submitted to HIV-I infection which developed into AIDS, with similar patterns to those observed in real conditions. Likewise, it was tested the effect of the soluble immune mediators in several events.

Simulation of other artificial systems, with heterogeneous physical environments and populations, are possible through the object-oriented support layer. This is accomplished by the redefinition of the specific genes and operators. Moreover, since twofold agent-environment interaction is possible, it can be used to simulate physical phenomena effects. Such flexibility is already demonstrated in the simulation with success of the immune response of the CD4+ T Lymphocyte Sub-Populations as described in [37].

The underlying physical medium can also be modeled as a complex adaptive system, enabling the simulation of detailed environment features, such as lymph nodes.

A possible extension to the current system, would aim one current drawback: the runtime redefinition of new models for both agents and environment. To offset this, a special-purpose language script containing agent rules and site local processing, among other settings, could be used, using a similar approach to that proposed in [5].

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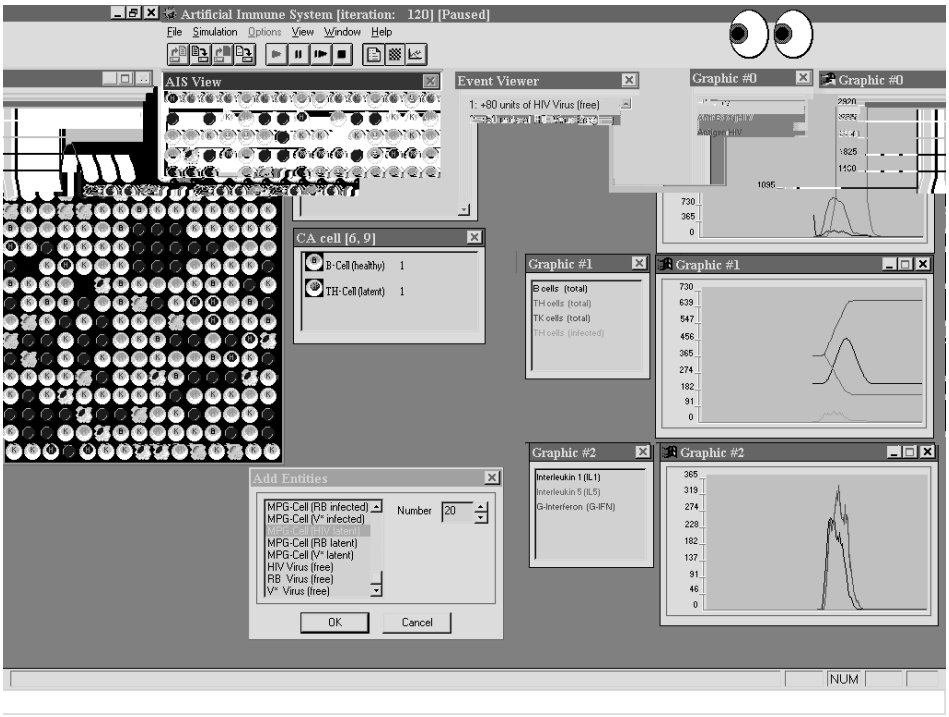

Fig. 16. Screen dump from an AIS simulation. Here we can see the environment lattice and the agents within it, where some of their partial state is shown. Some quantitative graphics are also available along with other information**.**

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