Do Artificial Immune Systems Model Immune Cognition?

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ABSTRACT

Researchers in cognitive science struggle to find a computational model that best represents cognitive phenomena for the latter are extremely complex and their mechanisms are not well understood. The biological immune system, in turn, features intrinsic cognitive characteristics. As a consequence, computational models of the immune system are capable of naturally incorporating many of these abilities with advantages over more traditional models of cognitive systems. The main purpose of this study is to highlight the cognitive aspects of artificial immune systems in parallel/contrast with more traditional models of cognition.

1. INTRODUCTION

Research in Artificial Intelligence (AI) started with the goal of replicating human level intelligence in a machine 8. Early hopes to achieve it diminished as the magnitude and difficulty of that goal was appreciated. Traditional models of AI, namely physical symbol systems 8 assume that the mind functions in much the same way as computers do and that cognitive processes are rule governed manipulations of internal symbolic representations. This broad idea has dominated the philosophy and the rhetoric of cognitive science – and even, to a large extent, its practice – ever since the field emerged 8. This depiction of learning as the rule-governed updating of a system of sentences or propositional attitudes encountered a wide range of failures. For starters, even the best of the rules proposed failed to reproduce reliably our preanalytic judgments of credibility even in the simplest of cases 8. Even in the human case the depiction of one's knowledge as an immense set of individually stored 'sentences' raises a severe problem concerning the relevant retrieval or application of those internal representations, broadly known as the "Frame Problem" in AI 8. Thus we are led rather swiftly to the idea that there is a level of representation *beneath* the level of sentencial pr propositional attitudes, ad to the correlative idea that there is a learning dynamic that operates primarily on sublinguistic factors 8. Moreover, it is no longer true that we lack a comparably compelling alternative approach to physical symbol systems. There have been some striking theoretical developments and experimental results with cognitive neurobiology and 'connectionist' AI 8. These models, however, utilize neural networks as the most natural and straightforward model of cognitive system because of the obvious reason that they have the brain as inspiration. This led to some pitfalls that can be avoided by using the immune system as model.

Many researchers have pointed out the cognitive abilities of the immune system 8, 8, 8, 8[refs], giving rise to a field of research dubbed cognitive immunology 8, 8. Some have proposed that the entire immune system is a cognitive system, as opposed to the contemporary model most broadly accepted, the clonal selection theory proposed by Burnet 8, for which he received the Nobel Prize. Nonetheless, in its initial formulation, the theory failed to explain autoimmune diseases, pregnancy, tumors, vaccination, among others. In view of these problems, many tried to patch it up with the addition of co-stimulatory signals 8 and/or interactions among the immune cells. Niels Jerne proposed one of the most controversial alternative theories, the immune network 8, which paved the way to cognitive immunology and to the view of the immune system as a cognitive system. The complexity of the immune system is sometimes compared to that of the brain in many respects 8, especially due to the cognitive abilities of the immune system such as: learning, adaptation, associative memory, self-regulation, pattern recognition, maintenance of diversity, among others.

Artificial Immune Systems (AIS) are adaptive procedures inspired by the biological immune system for solving several different problems 8. Dasgupta defines them as "a composition of intelligent methodologies, inspired by the natural immune system for the resolution of real world problems 8".

The next section is devoted to introducing the most important models of cognition. It is followed by some basic concepts and models of immunology which will lay the theoretical groundwork for the rest of this paper. Next, the concept of immune cognition, along with its different perspectives, is briefly reviewed. Then, I discuss models from immunology used as inspiration to design artificial immune systems. We conclude by considering the appropriateness of utilizing the immune system, by means of artificial immune systems, as model for cognitive systems in contrast with the more traditional neurological view along with its counterpart, artificial neural networks and by indicating future trends and enhancements to this research.

2. COGNITIVE MODELS

The three most traditionally and broadly accepted models of cognitive systems will be briefly presented and discussed below.

2.1 Physical Symbol Systems

In one of the most well known presentations of the computational conception of cognition, Allen Newell and Herbert Simon 8 hypothesized that "physical symbol systems contain the necessary and sufficient means for general intelligent action," where a physical symbol system is "a machine that produces through time an evolving collection of symbol structures 8." Newell states that this concept has emerged from his growing experience and analysis of the computer and how to program it to perform intellectual and perceptual tasks 8. Bearing this in mind, computational systems can be categorized as abstract state-dependent systems whose states are constituted in part by configurations of symbol types, whose time set is the integers, and whose rule of evolution specifies sequences of such configurations 8. This means that, at any given time, it must contain an appropriate configuration of *tokens* of the symbol types, and it must change sequentially from one such

configuration to another in accordance with the rule of evolution 8. In other words, taking cognitive systems to be state-dependent systems that proceed from one configuration to the next is part and parcel of a general vision of the natures of cognitive systems. For computationalists, the cognitive system is basically the brain, which is a kind of control unit located inside a body which in turn is located in an external environment. The cognitive system interacts with the outside world via its more direct interaction with the body. Interaction with the environment is handled by sensory and motor transducers, whose function is to translate between purely physical events in the body and the environment and the symbolic states that are the medium of cognitive processing 8.

2.2 Connectionist Architectures

According to Paul Smolensky's view, the true commitment of connectionism is to a very general formalism for describing mental representations and mental processes. He states that, according to this view, mental processes are vectors partially specifying the state of a dynamical system (the activities of units in a connectionist network), and that mental processes are specified by the differential equations governing the evolution of that dynamical system 8. According to the most traditional view, connectionist models, in turn, are large networks of simple parallel computing elements, each of which carries a numerical *activation value* which it computes from the values of neighboring elements in the network, using some simple numerical formula. The network elements, or *units*, influence each other's values through connections that carry a numerical strength, or weight. The influence of each unit on the others is its activation value times the strength of the connection between them 8. Within this framework, connectionist models can be characterized as a particular subcategory of state-dependent systems 8.

The term connectionism is usually applied to neural networks. There are, however, many other models that are mathematically similar, including classifier systems, immune networks, autocatalytic chemical reaction networks, and others. In view of this similarity, it is appropriate to broaden the term connectionism. Farmer 8 defines a connectionist model as a dynamical system with two properties: (1) The interactions between the variables at any given time are explicitly constrained to a finite list of connections. (2) The connections are fluid, in that their strength and/or pattern of connectivity can change with time.

2.3 Dynamical Systems

Dynamical systems were proposed as an alternative to the computacional conception of cognitive systems. Dynamical systems are defined as a subcategory of state-dependent systems 8. One of the most pertinent contrasts between dynamical systems and physical symbol systems is that the states through which the former evolve are not configurations o symbols but rather numerically measurable quantities. According to Tim Van Gelder 8, the dynamical hypothesis in cognitive science is the exact counterpart to the computational hypothesis: cognitive systems are dynamical systems and cognition is state-space evolution in such systems.

3. IMMUNOLOGICAL CONCEPTS

This section presents some basic immunological concepts in order to introduce the reader to the jargon and formalization adopted.

The immune system of vertebrates is an intricate collection of distributed cells, molecules and organs that altogether play the important role of maintaining a dynamic internal state of equilibrium in our bodies. Its complexity has been compared to that of the brains in many respects: immune systems are capable of recognizing foreign and internal signals; controlling the action of immune components; influencing the behavior of other systems, such as the nervous and the endocrine systems; and, most importantly, learning how to fight against disease causing agents and extracting information from them.

The immune system has an ability to identify specific events and changes in the body. The immune system's environment is the body. It interacts on the cellular/molecular level. To do this, it has many types of cells as well as effector and signaling substances, many of which are yet to be identified and understood. However, in general the population of cells that make the immune system can be characterized as the populations of cells known as lymphocytes. The two most important groups of lymphocytes are called B cells and T cells.

Both of these cell families have a unique ability the create receptors, which, though they all originate from the same genetic material, use different combinations of this material to create an immense variability in their final form. The shape of the receptor, which like all proteins is based on the sequence of a certain gene, implies the shape and type of molecule that will activate the receptor. Therefore, this genetic variability gives the immune system the potential ability to have receptors that can identify a near infinite number of molecular shapes. The molecules that immune receptors identify are commonly known as antigens. The region within the antigen to which they attach is known as an epitope. A single antigen may have several different epitopes.

The receptors of B cells identify extracellular substances. The receptors of T cells identify intracellular substances by interacting with specialized antigen presenting proteins known as major histocompatability complex (MHC) receptors 8, which are expressed on the surface of every one of the body's cells. MHCs present fragments of intracellular proteins, in effect mirroring the internal state of the cell. Together, T cells and B cells can identify most intra- and extracellular substances. The immune system's identification and reaction to a pathogen or other immune events is dependent on mutual reaction by both T cells and B cells to that event 8.

The potential repertoire of receptors is immense, between 10^{11} for B cells and 10^{16} for T cells 8. Because (in mice) the immune system contains only about 10^{8} of each of the types of cells and every single cell has only one type of receptor, it is obvious that the actual repertoire is smaller. If the immune system were to have a repertoire built of every potential receptor it can generate, then in a rat, for example, this would necessitate having a spleen 70 times the size of the rat's entire body 8. The immune system can be divided into innate immune system and adaptive immune system, composed of diverse sets of cells, molecules and organs that work in concert to protect the organism.

3.1 The Innate Immune System

The innate immune system is very important as a first line of defense against several types of pathogens and is also crucial for the regulation of the adaptive immune system. Cells belonging to the innate immune system are capable of recognizing generic molecular patterns (a type of molecular signature) that are only present in pathogens, and can never be found in the cells of the

host. Once a pathogen has been recognized by a cell of the innate immune system, this cell signals (through chemical messengers) other immune cells, including those of the adaptive immune system, to start fighting against the pathogen. Therefore, the innate immune system plays a major role in providing co-stimulatory signals for the adaptive immune system. Co-stimulatory signals are usually provided by the innate immune system when the organism is being damaged in some way. For the most types of pathogens, the adaptive immune system cannot act without the co-stimulatory signals provided by the innate immune system. However, not all pathogens can be recognized by the innate system. Some specific pathogens are only recognized by cells and molecules of the adaptive immune system, also called specific immune system.

3.2 The Adaptive Immune Response

The adaptive immune system posses some particular features that are important from a computational perspective. For instance, it can adapt to those molecular patterns previously seen and it generates and maintains a stable memory of known patterns. After a certain pathogen has been eliminated by the adaptive system, the innate system plays a role in signaling the adaptive system that the foreign agent has been defeated. Another way the innate immunity is important for the adaptive immunity is in that the latter usually requires some time before it starts acting. Thus, the innate immune system tries to get the pathogen at bay until the adaptive immune system can act, but the innate system by itself is usually not capable of removing the infection.

Once the adaptive immune system is prepared to act, it can adapt to the invading pathogen and create specific molecular patterns to fight against the same or a similar future infection of this type. The mechanisms underlying this adaptability of the immune system have also been broadly explored in AIS, and these will be discussed later.

Last, but not least, there are theories that suggest the immune system is a dynamic system whose cells and molecules are capable of interacting with each other. This viewpoint establishes the idea that pathogens are responsible for modifying the structure of a dynamic immune system, while the other more traditional perspectives suggest that the immune system is composed of discrete sets of cells and molecules that are only activated by pathogens. This section reviews some basic immune theories and principles that have been used for the design and application of artificial immune systems, including the more controversial immune network theory. The adaptive immune system is emphasized due to its adaptation, learning, and memory capabilities.

Several theories were proposed as attempts to explain how the immune system copes with antigens. It were M. Burnet and D. Talmage who in the mid 1900s proposed and formalized the clonal selection theory of adaptive immunity 8, broadly accepted as an explanation of how the adaptive immune system responds to pathogens. Together with the theory of affinity maturation of antibodies 8, clonal selection forms the core of an adaptive immune response, and both have been used in the literature of artificial immune systems to design adaptive systems for problem solving.

3.3 The Clonal Selection and Affinity Maturation principles

When a pathogen invades our bodies, some of our immune cells that recognize this pathogen will start replicating, a process during which mutation occurs. One interesting aspect of the cellular reproduction (cloning) process in the immune system is that cells are subjected to error during cloning. In this case it is a mitotic process of cell division that may result in errors in the progeny cells generated. Also, the mutation rate is proportional to the affinity the immune receptor has with the pathogen recognized.

In summary, clonal selection and expansion together with affinity maturation occur as follows. Our immune system is composed of a huge number of cells presenting receptors on their surfaces. These receptors are responsible for binding with portions of pathogens, known as antigens, and signaling other immune cells to eliminate the marked (recognized) pathogens. But the invading pathogens replicate themselves inside our bodies thus increasing the amount of damage being caused to our organism. One way the immune system evolved to fight against infection was by replicating our immune cells so as to cope with the replicating pathogen. But the replication of immune cells is not perfect; errors occur with a rate proportional to the quality of the recognition between the immune receptor and the pathogen recognized. Those mutated cells with high affinity with the pathogen are then selected and maintained in a repertoire called memory. Figure 1 summarizes the clonal expansion and affinity maturation processes.

The clonal selection principle proposes a description of the way the immune system copes with the pathogens to mount an adaptive immune response. The affinity maturation principle is used to explain how the immune system becomes increasingly better at its task of recognizing and eliminating these pathogens (antigenic substances). The immune network theory hypothesizes the activities of the immune cells, the emergence of memory and the discrimination between reactive and tolerant regions in the shape-space.

3.4 Negative Selection

One question that for long has intrigued scientists in various fields is that of how the immune system differentiates between the cells of the organism, known as self, and the foreign elements capable of causing disease, known as nonself. There are various theories that try to approach this question, and one of these involves the negative selection of T-cells within the thymus. Other less orthodox proposals are the idea that the immune system evolved to discriminate between infectious nonself and noninfectious self 8, and the Danger theory that suggests the immune system is capable of recognizing stress or damage signals 8.

When an immune cell encounters an antigen, several outcomes might arise. For instance, it has been discussed that if the antigen is nonself, i.e. disease-causing, then the clonal expansion of those cells successful in recognizing and binding with the antigen will occur. But this is not the whole picture. In the case an antigen is recognized by an immune cell while it is patrolling the organism for nonself, a second signal, also called co-stimulatory signal, from other immune cells is required before an adaptive immune response can be launched.

What if the antigen is a self-antigen? There are a few possibilities in this case and only the negative selection of T-cells within the thymus will be considered here. In a simplified form, if a self antigen is recognized by an immature T-cell within the thymus, this cell is purged from the repertoire of T-cells, else it becomes an immunocompetent cell and is released to circulate throughout the body in the search for nonself antigens. This

process, caled thymic negative selection of T-cells or simply negative selection, is only possible because the thymus is protected by a blood-thymic barrier that filters out any molecule that does not belong to self. Thus, all molecules within the thymus are self molecules, and the immature T-cells learn to be tolerant (not respond to) to the self molecules while within the thymus.

3.5 The Immune Network Theory

Jerne 8 formalized in 1974 what is to date known as the immune network theory. His great insight was that the immune system is not only a reactive system that remains at rest until an antigen invades the organism. He suggested that some portions (idiotopes) of the receptors of our immune cells could be recognized by other immune cells and molecules. This would result in an immune system that is always dynamic; that is, an immune system that does not wait for external stimulation in order to act.

One question that may be raised by this assertion is: "if the immune system recognizes our own cells, why does it not react to our own cells?" The suggestion proposed at that time was that a suppressive mechanism would control "self-recognition" while an activation mechanism would guide the immune response. However, these mechanisms were neither clearly accounted for in the theory nor clearly observed experimentally. The network theory generated a lot of debate within theoretical and experimental immunology.

In summary, the network theory suggested that the immune cells and molecules are capable of recognizing each other and antigens. This recognition results in variations in the concentration and affinity (DNA structure) of immune receptors. These variations are a function of several factors: 1) the network suppressive effects, 2) the network activation effects, 3) the death of unstimulated cells, and 4) the recruitment of new cells and molecules from the immune repertoire.

3.6 The Danger Theory

With a conceptually different viewpoint, Polly Matzinger 8, 8 introduced what came to be known as the danger theory. In essence, the danger model adds another layer of cells and signals to the self/nonself discrimination models. It proposes that antigen-presenting cells (APCs), such as those exposed to pathogens, toxins, mechanical damage, etc., are activated by the alarms caused by these phenomena.

The danger model tries to answer one of the fundamental questions in immunology: How is self-tolerance induced? It suggests that the immune system is more concerned with damage (preventing destruction) than with foreignness. It takes into account issues like what happens when bodies change (e.g., through puberty, pregnancy, aging, etc.); why are there T- and B-cells specific for self antigens; why do we not mount immune responses to vaccines; why neonates are easily tolerizable; why silicone, well boiled bone fragments, or solitary happens do not elicit immune responses; why do we fail to reject tumors; and so forth 8, 8.

A puzzling question is how to distinguish between dangerous and nondangerous. At the same time there are several foreign things that are dangerous, such as bacterial toxins, viruses, worms, and others, there are also dangerous 'self', such as tumors, and non-dangerous foreign, such as beneficial bacteria and nonlytic viruses. The new danger theory proposes that antigen presenting cells are activated by danger/alarm signals from injured cells, such as those exposed to pathogens, toxins and mechanical damage. The mechanisms of immune activation would be a consequence of cell/tissue damage. Cell death is not always a result of parasitic attack. It is a normal event during embryonic development, formation and death of hematopoietic cells, maturation and expulsion of oocytes, etc. In such cases, death is controlled, usually apoptotic, and cells that die by these normal programmed processes, are usually scavenged before they desintegrate. By contrast, cells that die by stress or necrotically release their contents in the surroundings and these serve as (danger) signals.

The key issue is that danger signals are not sent by normal (healthy) cells, only by injured tissues. The danger signals can be active or passive 8. Abrupt changes in the condition of a cell, like, for instance, temperature variation or infection, elaborate a series of heat shock proteins that aid their recovery, and serve as danger signals. Internal molecules, normally not secreted, may also serve as a danger signal; thus, any cell damage caused by a cut, bruise and infection, can be noted.

4. COGNITIVE IMMUNOLOGY

Survival and maintenance in living organisms, from invertebrates to mammals, are assured by a variety of evolutionary conserved mechanisms. From this point of view, a critical role is played by cognitive systems, capable of acquiring and elaborating information from the environment (external world), as well as from the internal milieu (internal world). Three biological systems, the immune system (IS), the nervous system (NS), and the endocrine system (ES), evolved to play such a fundamental role for complex living organisms. These systems are deeply interconnected among them, and share some basic architectural and organisational characteristics, despite having specific peculiarities.

In the case of foreign antigens (pathogens) danger signals are delivered as molecules detected by Toll-like receptors while damage signals as "alarming" cytokines due to local inflammatory processes. Thus, it is the association of foreign molecularpatterns owned by pathogens with the danger and/or damage molecular signals that is able to trigger the immune response, allowing to put forward the concept that the innate IS is sensitive to and perceives the context. The goal is to emphasize that the immune system knows what it is looking for when it encounters a pathogen, i.e., its internal organization endows it with a certain intentionality. Niels Jerne 8 (1974, 1984, 1985), with his immune network theory, is considered to be the true proponent of the cognitive model of the immune system 8.

Several research schools investigate what is now called immune cognition under basically three different perspectives: 1) the self-recognition view; 2) the self-assertion view; and 3) the multi-systemic view. This section reviews some works from the immunology literature that explicitly discuss the immune cognition.

4.1 The Self Recognition View

Under this perspective, immune cognition is based upon the principle that the immune system is capable of distinguishing between what belongs to the organism, known as self, and what does not belong to the organism, known as nonself; a principle called self/nonself discrimination. In this case the immune system is a recognition/action system that acts according to foreign (nonself) stimulation. This is the most orthodox view of

the immune system still accepted by a large, maybe the largest, number of researchers in immunology. It came into the scene about the 1950s with Burnet's formalization of the clonal selection principle 8.

The recognition and classification of foreign elements to the organism implicitly re-quires that some immune components are performing this identification. Recognition is a perceptive event and, as such, it has to be sustained in some sort of cognitive apparatus 8. This viewpoint reflects the richness hidden in terms like recognition, learning and memory; properties pertinent to the immune system. Actually, all these properties were brought into immunology based on the parallel with nervous cognition, which is even more striking under the network approach for the immune system, as will be discussed shortly.

To I. Cohen 8, 8 a cognitive system is an intentional system; that is, one capable of extracting information from the environment by exploiting the knowledge contained in the system itself. Thus, a cognitive system is not a passive information processor or memory device, it is designed to manipulate particular information sensed from the environment 8. He also proposed the concept of an immunological homunculus as an internal image of the self, acquired by the early recognition of self. (In the original clonal selection model introduced by Burnet, it was proposed that self-reactive lymphocytes were deleted early in life.) The immunological homunculus is rooted on the idea that the immune system will be capable of performing its task more efficiently through the gathering and processing of information if it is endowed with an internal representation of the environment in which it is inserted. Pathogens are recognized as non-self because they are presented in a context that indicates their pathology. Under this viewpoint, self is no longer an entity; rather it emerges dynamically in a self-identification process that changes continuously along the lifetime of an individual.

4.2 The Self Assertion View

This view does not see the immune system as behaving distinctively with self and nonself or according to any dichotomy imposed a priori and from the outside 8. In this case the immune system is viewed as a dynamic system that does not require foreign (nonself) stimulation to present activity. There is no fundamental difference between self and nonself. This is known as the self-assertion view of the immune system and is in most of its presentations rooted on the immune network theory.

A vast number of authors have discoursed about the cognitive nature of the immune network theory 8, 8, 8, 8, 8, 8, 8, 8, 8. The claim in most cases is that global cognitive properties of the immune system like learning, memory, adaptation, self-sustainability, etc., cannot be understood through the analysis of individual components. As the network theory suggests an immune system composed of sets of cells and molecules interconnected via communication (affinity) links, the network approach becomes quite suitable to the study and understanding of cognitive phenomena in the immune system.

The immune network theory proposes that portions, called idiotopes, of the receptor molecules located in and around their variable regions can be recognized by the paratopes on other receptors. As a result, cells and molecules from the immune system can recognize each other. Under this perspective, the immune system is composed of a universe of "internal images" of all possible antigens, which are only recognized for they are expressed in a language known to the system, and the immune system becomes self-defined; that is, it is designed to know itself. These are the two roots of the cognitive view of the network theory.

4.3 The Multi-Systemic View

The immune system is a vital system integrated with other bodily systems, and, as such, it does share recognition, activation, effector and adaptation mechanisms. There are in-creasing evidences of the interdependence between the immune system and other systems through messenger molecules, neurotransmitters and hormones. Besides, there are functional analogies between the immune system and other systems. For instance, the immune and the nervous systems perceive and recognize the environment, and then decide what mechanisms to put into action in order to operate. This is the multi-systemic perspective on immune cognition.

Blalock 8 approached the immune system as a sensorial system, such as the nervous system, but he attributed cognition only as a process resulting from stimuli like physiological, emotional, etc. He proposed that the immune system is capable of recognizing and responding to stimuli that cannot be perceived by the nervous system like bacteria, viruses and tumors. These stimuli would go unnoticed if not for the immune sys-tem. A virus cannot be seen by a naked eye, it cannot be smelt or tasted, it makes no noise, but it can be perceived by the symptoms it causes. This occurs through the recognition of this stimulus by immune cells, which convert it into chemical information such as hormones, neurotransmitters and cytokines. These signals are received by the nervous and the endocrine systems resulting in psychological and physiological changes. Apparently, the sensorial operation of the immune system imitates the neuroendocrine system in the sense that a specific stimulus promotes a particular response that results in a physiologic response. Due to this capability of recognizing and responding to stimuli that can-not be perceived by our sensorial systems, Blalock (1994) suggested the immune system is our sixth sense.

Besendovsky & del Rey 8 followed the same approach as Blalock 8 arguing that the intercommunication between the immune and the neuroendocrine systems implies that the immune system is a receptor sensorial system. However, the sensory function of the immune system does not imply that the central nervous sys-tem will always react to signals derived from immune cells. A neuroendocrine response to immune signals occurs in a threshold-dependent manner, and only seldom do such responses become cognitive. A cognitive sensation is expected to be more often related to stimuli that occur as a consequence of the disease rather than to the elicited immune response itself. The authors also suggested another interesting phenomenon that might reflect the reception of signals from immune cells at the central nervous system level: the behavior condition of certain immune responses. It implies that the immune system is capable of informing the brain about the effect of the stimuli, and the brain, in turn, would mediate the conditioned stimulation or inhibition of the immune response.

4.4 The Immune Cognitive System View

Finally, there is the model of the immunological system as a whole functioning as a cognitive system 8. There is an especially widespread debate on the way in which the immune system differentiates between the molecular patterns of the body and foreign pathogens. The clonal selection theory, states that anything that an immune cell receptor identifies is a foreign pathogen. According to the clonal selection theory, this state of

affairs is brought about in the following way: during embryonic development immune cells are created randomly, each reactive to a different antigen. Those cells bearing receptors that bind to self antigens at a certain level of affinity or above are eliminated. This is known as negative selection. At the end of this process any receptors that remain can only be activated by foreign pathogens.

Several generally known aspects of immune detection, agreed on even by the most ardent supporters of the clonal selection theory, seem to imply that the immune system is working as a cognitive system: first, the need for costimulation of B cells and T cells for immune reaction 8, and second, the fact that B cells are reacting to extracellular information, whereas T cells react to intracellular information. Together these appear to imply an immune reaction to patterns and context.

Treating the immune system as a cognitive system, the idea of building a repertoire in the way suggested by the clonal selection theory becomes less plausible. The immune system's environment is built completely of cells both endogenous and exogenous, which at the time of encounter are residing in the body. Also, all of this cellular and viral life is built of similar building blocks. There is no intrinsic molecular signal that differentiates between the organic substances of our body and those of other organisms. Removing all receptors to self amounts to removing all receptors to all of the things that are common to all cellular life. Building a system that needs to recognize the important aspects of this environment but is blind to the general properties (which are those things that are ubiquitous in the environment) is like building a human visual system that can not become aware of edges.

Uri Hershberg and Sol Feroni 8 suggest a model of the immune system as a cognitive system. This implies several things about the way the immune system is primed and how it detects its environment. The priming of the system and building of the achieved set of representations starts by fulfilling innate systemic biases or tendency. In this case, this would probably be a genetically transferred tendency to present certain protein examples that are used to build the receptor repertoires. These useful examples would, as in vision and language, be examples of the general properties of the living molecular environment. They should, therefore, be examples of self that cause a positive selection of receptors with at least some minimal affinity to these examples.

The adult repertoire of immune receptors is created by a combination of positive and negative selection using specific molecular examples of self. Part of the reason that the clonal selection theory is being forced to change is that positive selection is apparently important for the creation of the mature repertoires in both B cells and T cells. T cells must have a minimal affinity for at least one self antigen —MHC receptors— if they are to function.

5. ARTIFICIAL IMMUNE SYSTEMS

The literature is rich with works using particular aspects and principles of the immune system to design new algorithms or improve existing techniques for problem solving. However, given a suitable representation for the immune cells and molecules, and how to evaluate their interactions, it is possible to identify some general-purpose immune algorithms. These algorithms can be separated into two classes: population-based and network-based. The first class involves all algorithms that do not take into account the immune network, and the network-based algorithms are all those inspired by the network theory of the immune system. Three main classes of algorithms will be reviewed here:

- Negative selection: used to define a set of detectors (e.g., attribute strings) to perform, mainly, anomaly detection;
- Clonal selection: used to generate repertoires of immune cells driven by antigens. It regulates the expansion, genetic variation, and selection of attribute strings;
- Immune network models: used to simulate dynamic immune networks;

6. CONITIVE TASKS PERFORMED BY ARTIFICIAL IMMUNE SYSTEM MODELS

6.1 Negative Selection

One of the main functions of the thymus is to promote the maturation of T-cells. Immature T-cells, generated in the bone marrow, migrate into the thymus where some of them differentiate into immunocompetent cells (cells capable of acting during an adaptive immune response), and others are purged from the repertoire due to a strong recognition of self. This process of eliminating cells whose receptors recognize self is known as negative selection. The thymic negative selection has to guarantee that the T-cell repertoire that leaves the thymus and goes to the periphery does not contain cells that recognize self cells and molecules. Thus, the immature T-cells that maturate and leave the thymus become a sort of change or anomaly detectors. The thymic negative selection has inspired the development of a negative selection algorithm with applications focusing, mainly, on anomaly detection. There are two main versions of this algorithm: one for binary shape-spaces 8 and another for real-valued shape spaces 8. Negative Selection Algorithms are in line with the self recognition view of the immune system. These algorithms are able to perform binary pattern classification through the extraction of the relevant features of the data used for it to learn what is self. They perform tasks very much like two-layer-perceptron neural networks 8.

6.2 Clonal Selection Algorithms

The immune system is a complex of cells, molecules and organs with the primary role of limiting damage to the host organism by pathogens, which elicit an immune response and thus are called antigens. One type of response is the secretion of antibody molecules by B cells. Antibodies are receptor molecules bound on the surface of a B cell with the primary role of recognizing and binding, through a complementary match, with an antigen. Antigens can be recognized by several different antibodies. The antibody can alter its shape to achieve a better match (complementarity) with a given antigen. The strength and specificity of the antigen-antibody interaction is measured by the affinity (complementarity level) of their match. The clonal selection principle is used to describe the basic features of an adaptive immune response to antigens.

Clonal selection algorithms 8 take advantage of the self recognition view of the immune system. These algorithms are able to perform pattern recognition tasks, classification and clustering by partitioning the shape space much like MLP neural networks 8.

6.3 Immune Network Models

The immune network theory sounds very appealing for any researcher on computational intelligence and engineering background (and many others). First, it suggests a dynamic system capable of presenting interactions with the system itself and the external environment. Secondly, the capability of adjusting the system (network) structure to the environmental challenges and adjusting the parameters of the system to this environment is interesting from an engineering perspective. The network theory corresponds to another inspiration from the immune system to engineer a computational tool for problem solving. It is most natural to view the immune system as a sort of pattern recognition device; as was the first version of the clonal selection algorithm. The same may happen with the immune network theory. The idea was thus to implement an "artificial immune network" to perform pattern recognition. This was also a natural step for a researcher with background on neural networks, for ANN are known to be good at solving pattern recognition and function approximation problems.

Theoretical immunologists had already been modeling the immune network using ordinary differential equations to account for the variations in concentration and sometimes affinity of immune cells 8. Others developed an immune network more akin to neural networks, that is, adapted (trained) according to an iterative procedure of adaptation. The aiNet 8 is a discrete artificial immune network whose main role is to perform data clustering by following some ideas from the immune network theory, the clonal selection, and affinity maturation principles. The resulting self-organizing system is an antibody network that recognizes antigens (input data set) with certain (and adjustable) generality. The aiNet clusters will serve as internal images (mirrors) responsible for mapping existing clusters in the data set into network clusters. These clusters map those of the original data set. Notice also that the number of antibodies in the network is much smaller than the number of data samples, characterizing an architecture suitable for data compression. Finally, the shape of the spatial distribution of antibodies follows the shape of the antigenic spatial distribution.

The aiNet model can be classified as a connectionist, competitive and constructive network, where the antibodies correspond to the network nodes and the antibody concentration and affinity are their states. The learning mechanisms are responsible for the changes in antibody concentration and affinity. The aiNet general structure is different from neural network models 8, though, if one considers the function of the nodes and their connections. In the aiNet case, the nodes work as internal images of ensembles of patterns (thus representing the acquired knowledge), and the connection strengths describe the similarities among these ensembles. On the other hand, in the neural network case, the nodes are processing elements while the connection strengths may represent the knowledge.

Immune network algorithms are very much in line with the self assertion view of the immune system. These models have been shown to perform clustering, adaptive classification and pattern recognition tasks, knowledge extraction, hierarchical clustering, among others.

7. CONCLUSIONS

It is becoming clear that the field of immunology is approaching a paradigm shift. It is agreed by most researchers that the immune system is a complex system both in its composition and its behavior. However, the most popular ideas of immune function treat the immune system in a mechanistic and reductionist manner. According to the clonal selection theory the immune system's function is to defeat pathogens. The immune system identifies foreign antigens and destroys them. The identification of the foreign is made possible by removing, in the immune system's prenatal development, all receptors that recognize self. Anything that an immune receptor identifies "must be the enemy" 8. Countering this mainstream view are a growing number of voices that state the need to change the clonal selection theory or discard it, claiming that such a simplistic appraisal of the immune system's function and mode of action is untenable because, at the molecular level, we are closely related to the pathogens that invade us. There is a need to consider the immune system as a integrative system with the ability to see patterns and understand context 8, 8. It is in the context of this argument about the immune system that we present our theory of cognitive systems and claim that the immune system should be seen as such a cognitive system. The phrase "cognitive system" is used in many fields to describe the various faculties that we and other organisms use to perceive and interact with the world. Despite its widespread use, the phrase "cognitive systems" has not yet been defined in a way that can be applied to all of the cases in which it is used. We suggest the following criterion to differ between cognitive and noncognitive systems: In cognitive systems the perceptual sensitivities of the system are not preordained only by the plan of the system but need an interaction with their environment to define the system's exact sensitivities.

Cognitive systems are innately built with a tendency toward perceiving certain aspects of the environment. These tendencies are such that they cause the cognitive systems to be receptive toward seeing certain general properties of the environment and examples that embody them. However, the cognitive system will only acquire general properties that are corroborated in its initial interactions with the environment. The definition of general properties by cognitive systems is something that is not completely predetermined but rather defined through interaction with the environment; the environment's reinforcement is what defines the final set of general properties that the cognitive system uses to know its environment. Through specific interactions and based on the previous tendencies of the system certain general properties are corroborated by "useful examples" of these properties appearing in the environment. This corroboration leads to the formation of an achieved set of representations in the system. For instance, the knowledge of the general properties of visual stimuli is not something that we are born with; rather, it is acquired through the natural exposure to the environment. The process of learning the general properties is unsupervised and is based on the existence of useful examples for the general properties of naturally encountered visual stimuli. The general properties are those things that are both ubiquitous to the different stimuli and appear in many different meaningful contexts.

The current view of the immune system has developed over several decades from that of a rather mechanistic response-to-stimulus machine to that of a cognitive system capable not only of building a specific response but of making the decision whether to enact it or not. It does so by using information independent of the stimulus per se, and following a behavioral code evolved during phylogenesis and ontogenesis. As a result of the accumulated findings, the connections among lymphoid cells look more similar to those among neurons, and the

recognition/response follows rules similar to those defined by semiology for the human mind 8, 8.

Artificial immune systems perform the same tasks artificial neural networks under the very same connectionist philosophy with some advantages. They usually do not require training, but rather, undergo an unsupervised, self-regulated learning process. Thus, AISs partition the shape space preserving topology, maintaining diversity, being robust to noise, compressing the data, presenting intrinsic associative memory and adaptation. Finally, AISs can perform symbolic and vectorial manipulations depending upon the shape space, which may be discrete or continuous, binary, real-valued or symbolic. ANN models for connectionism are not necessarily the most appropriate to corroborate the connectionist view of cognition.

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