ARTIFICIAL IMMUNE SYSTEMS:
PART II – A SURVEY OF APPLICATIONS

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Technical Report
DCA-RT 02/00
February, 2000

Summary

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1. Introduction

The first part of this report (De Castro & Von Zuben, 1999) is intended to present the basic theory and concepts necessary for the development of immune-based systems. It brings an instructive introduction to the mammal immune system and depicts its most relevant aspects from the viewpoint of engineering. Mechanisms like the *clonal selection theory*, the *immune response* along with its *affinity maturation* process and the *immune network hypothesis* are emphasized. A few computational algorithms were developed and applied to several different types of problems in order to demonstrate how principles gleaned from the immune system can and must be used in the design of engineering tools for solving complex tasks. In addition, it is introduced an emerging area of research, called *immune engineering*. The artificial immune systems are comprised of several strategies, such as immune engineering algorithms, immune-based systems, immunogenetic approaches, and is supposed to include any technique developed using ideas from immunology.

In this second part of the report, it will be assumed that the reader is familiar with the immune system, so that no description about the basic immunological phenomena will be presented. If it is the case, the first part of the report might be consulted. In this text, we are going to make a brief description of several applications that used immune metaphors, or mechanisms, to solve problems which are usually dealt with *artificial intelligence* (AI) techniques. Artificial intelligence strategies were developed aiming at finding solutions to a broad class of problems, named complex problems, which could not be resolved by traditional methods, like *linear, non-linear, multi-objective and dynamic programming, search trees, graph theory* etc. As will be seen, some of the methods presented in this text constitute hybrid approaches, where AI techniques, like *neural networks*, *fuzzy systems* and most influentially *evolutionary strategies*, were combined with immune phenomena and/or metaphor leading to the emergence of new computational paradigms.

Our goal is to bring together many works involving the immune system as far as to list and detach the main characteristics and potential applicability of each of the methods presented. Very few details about the applications themselves and their results are given, instead a brief description, focusing on the coding schemes, evaluation functions and how the methods are viewed under an immune perspective are the contents of this text.

The methods are distributed by subject and/or application, but even if some of them might belong to more than one class, it will be put into a single category. The illustrations were taken or adapted from the original works presented in the listed literature, and some explanations might simplify the original ones in order to make this report a comprehensive survey. At last, to keep the original terminology and lists of symbols used by each author, we did not follow any standard in our descriptions.

1.1 A Pioneer Work

The paper by Farmer *et al.* (1986) is considered the pioneer work relating the immune system to other artificial intelligence approaches. They described a dynamical model for the immune system based upon the *immune network* hypothesis. This model consisted of a set of differential equations, together with a threshold to remove useless antibody types, and genetic operators to introduce new ones. They showed that the equations of motion for the immune system and a proposed learning classifier system assume the same form, illustrating that these equations can have a broad utility for learning.

In fact, they were right with relation to the application of their model for solving engineering problems. As will be seen along this text, their "artificial immune system" served as a source of inspiration for several other immune-based strategies.

The immune cell and molecules were represented as binary strings of various lengths. An antibody molecule was represented by its *epitope* and *paratope*, concatenated in a single string.

To model the fact that two molecules may react in more than one way, strings are allowed to match complementarily in any possible alignment. Equation (1) specifies the matrix of matching specificities m_{ij}

$$m_{ij} = \sum_k G\left(\sum_n e_i(n+k) \wedge p_j(n) - s + 1 \right), \tag{1}$$

where $G(x) = x$ for $x > 0$ and $G(x) = 0$ otherwise, $e_i(n)$ is the n-th bit of the i-th epitope, $p_j(n)$ is the n-th bit of the j-th paratope, $\wedge$ corresponds to the complementary matching rule (XOR operation),

and s is a matching threshold. If matches occur in more than one alignment, their strengths are summed.

To model the network dynamics, it is assumed N antibody types with concentrations $\{x_1,...,x_N\}$ and n antigens with concentrations $\{y_1,...,y_n\}$. The set of differential equations

$$\dot{x}_i = c\left[\sum_{j=1}^{N} m_{ji} x_i x_j - k_1 \sum_{j=1}^{N} m_{ij} x_i x_j + \sum_{j=1}^{n} m_{ji} x_i y_j\right] - k_2 x_i, \quad (2)$$

where the first term represents the stimulation of the paratope of an antibody type i by the epitope of an antibody j. The second term represents the suppression of antibody of type i when its epitope is recognized by the paratope of type j. The parameter c is a rate constant that depends on the number of collisions per unit time and the rate of antibody production stimulated by a collision. Constant k_1 represents a possible inequality between stimulation and suppression. The third term models the antigen concentrations and the last term models the tendency of cells to die (natural death rate, k_2).

Genetic operators, like *crossover*, *point mutations* and *inversion* were used to generate new antibody types.

2. Robotics

Robots can be defined as programmable, multifunctional manipulators designed to move material, parts, tools, or specialized devices through various programmed motions for the performance of a variety of tasks. Nowadays, one of the most difficult tasks in robotics is the so-called *autonomous navigation problem*, where a robot, or a set of robots, has to perform certain tasks without any external guidance. In this section, we will describe how immune principles are being applied to the autonomous navigation problem.

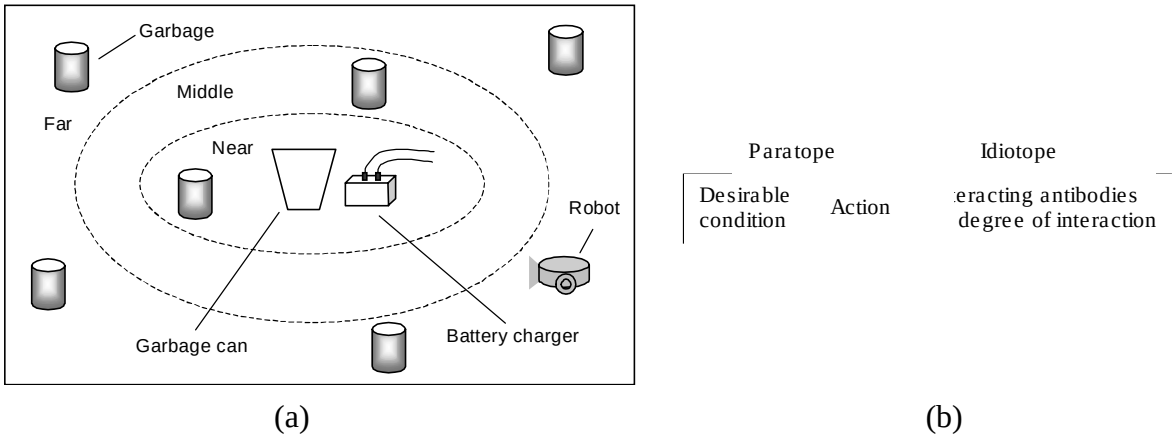
2.1 Behavior Arbitration Mechanisms

The main works of Ishiguro *et al*. (1996, 1997) and Watanabe *et al.* (1998, 1999) focused on the development of a dynamic decentralized consensus-making mechanism based on the *immune network theory*. In their approach, "intelligence" was expected to emerge from mutual interactions among agents (called *competence modules*) and between a robot and its environment. The open questions they tried to solve were the construction of a mechanism that realizes appropriate arbitration (decision) among multiple modules and how to prepare these modules. Their method was evaluated on a garbage-collecting problem taking into account self-sufficiency (autonomy), i.e. a robot had to collect a set of garbage and put it inside a garbage can without running out of energy (battery level). Figure 1(a) illustrates the problem.

The robot, called *immunoid*, was assumed to consume energy at every time step, when loaded with garbage and when it collided with obstacles. The antigens were responsible for informing the existence of garbage (direction), obstacle (direction) and home base (direction and distance), and also the current internal energy level. A pair of desirable condition/action rules was assigned to the paratope of each antibody, and the ID-number of the interacting antibodies was assigned to their idiotopes (see Figure 1(b)). The desirable condition is the same as the antigen. The antibody concentration level allowed the selection of the antibodies for a given antigen. Such a scheme made the antibodies responsible for the correct acting of the robot. Their model included the concepts of *dynamics*, responsible for the variation of the concentration level of antibodies, and *metadynamics*, which maintained the appropriate repertoire of antibodies by incorporating new types and removing useless ones. The concentration of the *i*-th antibody (a_i) was given by Equation (3):

$$\frac{dA_i(t)}{dt} = \left[\alpha \sum_{j=1}^{N} m_{ji} a_j(t) - \alpha \sum_{j=1}^{N} m_{ik} a_k + \beta\, m_i - k_i \right] a_i(t) \ ,$$
$$a_i(t+1) = \frac{1}{1+\exp(0.5 - A_i(t+1))}, \tag{3}$$

where N is the number of antibodies, α and β are positive constants, m_{ji} and m_i denote affinities between **Ab** *j* and **Ab** *i* and between the detected antigens and **Ab** *i*, respectively. The first and second terms indicate stimulation and suppression from other antibodies, while the third term represents stimulation from the antigen. The fourth term corresponds to the natural death rate. The equation in the bottom is a squashing function aiming at ensuring the stability of the concentration.



(a) (b)

Figure 1: (a) Environment for testing the consensus-making algorithm based on immune networks. (b) Definition of an antibody.

2.2 Emergence of Collective Behavior

For a collective behavior to emerge, a set of agents must communicate with each other and with their environment. The objective of the system proposed by Jun *et al.* (1999) and Lee *et al.* (1999) was that a set of robots (agents) found and carried out tasks spread along a given environment. They used the *clonal selection principle*, together with the *immune network theory* and *B-T-cell interactions* to cooperatively control and select a group of behavior strategies for Distributed Autonomous Robotic Systems (DARS). The executing process of their method had to be robust enough to overcome dynamic changes in environmental conditions. The behavior of each robot had to be stimulated and/or suppressed by other robots.

In the DARS system, the robots have to individually understand the objective of the system, the environment, the behavior of other robots etc., and decide their own behavior autonomously to cooperate with other agents aiming at establishing and maintaining the order of the whole system. No central control is supposed to exist. The clonal selection algorithm was used for transmitting high quality strategies among robots, while the immune network of antibodies controlled the interactions among individual robots and the B-T-cell interactions regulated the adaptability of the agents to the changing environment. Table 1 summarizes the relationship between DARS and the immune system.

To improve the adaptability of their system, the authors proposed a modified set of immune network equations that took into account the functions of a helper T cell and a suppressor T cell:

Table 1: Relationship between DARS and the immune system.

DARS	Immune System
Environment	Antigen
Strategy of Action	Antibody
Robot	B-cell
Control Parameter	T-cell
Adequate	Stimulus
Inadequate	Suppression
Excellent Robot	Plasma cell
Inferior Robot	Inactivated cell

$$S_i(t) = S_i(t-1) + \left[\frac{\alpha}{N} \sum_{j=1}^{N} m_{ji} s_j(t) - \frac{\alpha}{N} \sum_{j=1}^{N} m_{ik} s_k + \beta\, g_i - c_i(t-1) - k_i \right] s_i(t) \ ,$$
$$a_i(t+1) = \frac{1}{1+\exp(0.5 - S_i(t+1))}, \qquad (4)$$
$$c_i(t) = \eta\,(1 - g_i(t)) S_i(t),$$

where S_i is the stimulus for antibody i, s_i is the concentration of antibodies, m_{ij} is the mutual stimulus coefficient, g_i is the affinity of **Ab** i with the antigen, α, β and η are positive constants and k is the natural death rate. c_i is the concentration of T-cells that control the concentration of antibodies. Depending upon g_i and S_i, c_i will take the role of a helper or suppressor T-cell.

3. Control

In modern control engineering a lot of effort is put into designing robust control algorithms that can meet the steadily increasing demands for high performance. The immune system learning mechanisms, like clonal selection and affinity maturation, together with its network dynamics, suggest successful applications of these metaphors to the control theory.

3.1 Identification, Synthesis and Adaptive Control

Krishnakumar *et al*. (1995) and Krishnakumar & Neidhoefer (1997a,b, 1999) defined the Immunized Computational Systems (ICS) that used the immune system metaphor along with computational (both hard and soft computing) techniques to attempt to reproduce the robustness and adaptability of a biological immune system. The strategy was tested on an autonomous aircraft control problem.

Their system constituted a hybrid structure whose building blocks, mimicking the immune building blocks, were composed of artificial neural networks, fuzzy systems and evolutionary algorithms. Their immune metaphor focused on the *clonal selection principle*, together with the *affinity maturation* of the immune response. Table 2 depicts their viewpoint of the trade-off between the immune system and the intelligent control theory. Figure 2 depicts the basic structure of their immunized computational system.

They used messy strings to form a population of CCS (changeable computational systems), which represented the **Ag** and **Ab** equivalents. Figure 3 exemplifies a few types of information that could be inserted in the strings that represented the immune molecules. A collection of building blocks was assembled together in order to generate a population of computational systems, which were subject to evolution through genetic operators and selection.

Table 2: Trade-off between the immune system and the intelligent control strategy.

Immune Response	Intelligent Control
Antigen is present in the system	Disturbance is present in the system
Innate immunity is the first line of defense	Robust feedback control (non-adaptive)
Ag presentation (by macrophages) cause T-cell response (adaptation)	A utility function translates the disturbances into an error function and presents it to the critic which starts the adaptation process
T-cells activate B-cell response (adaptation) to counteract antigen	The adaptive critics modify the controller parameters to counteract disturbances
For certain types of **Ag**, the B-cells are triggered without the help of T-cells but still with the help of some APC's	For certain classes of disturbances, the controller is adapted directly based on a utility measure

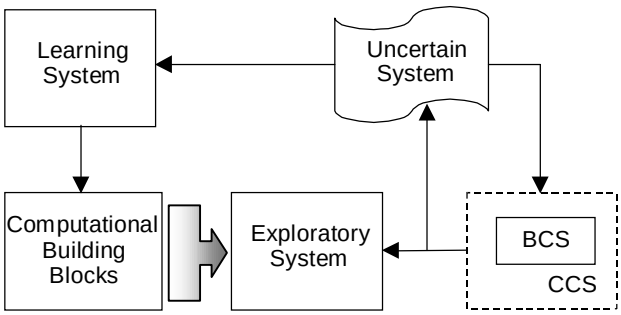


Figure 2: Immunized computational system structure. BCS corresponds to the base-line computational system (representing an average behavior of the uncertain system), and CCS corresponds to the changeable computational system (representing the variable region of the antibody and epitope equivalents).

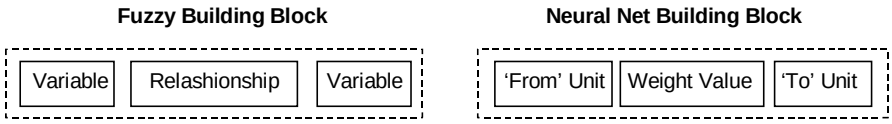


Figure 3: Encoding scheme for the case of a Fuzzy and a Neural Network building block. The parameter 'variable' can assume any linguistic value (altitude, speed, etc.), and 'relationship' represents any logical antecedent (AND, OR, etc.) or consequent (THEN). The neural net building block is responsible for describing the network architecture and weight values.

3.2 Sequential Control

Finding a proper execution sequence for a set of actuators such that the system achieves a desired state from a known initial state is the main goal of a sequential control approach. Ootsuki & Sekiguchi (1999) proposed a method for determining control sequences of a sequential control plant based on the immune system. They used the Petri Nets formalism and the *immune network theory* to develop their model.

The discrete dynamic behavior of the components of a sequential control plant was modeled as state machines structured as Petri nets. Hence, the determination of control sequences became equivalent to the determination of firing sequences for the Petri net models, which were decomposed into several sub-problems. The objective function of each sub-problem was set to satisfy constraints and minimize the objective function of a distributed (immune) network. The dynamics of the system was controlled by a set of differential equations, which described the interactions among the network elements. Their approach was compared to a conventional one, and its performance was superior for larger models with distributed characteristics and high degree of freedom in its components.

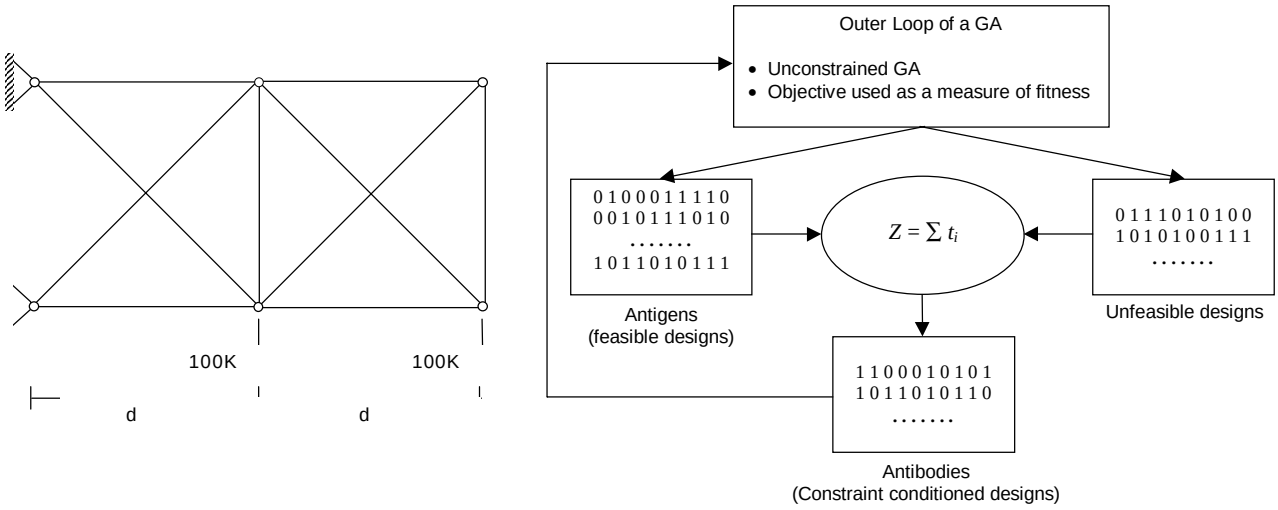
4. Optimization

Optimization is the task of finding the absolutely best set of admissible conditions to achieve a certain objective, formulated in mathematical terms. Problems in optimization arise in a broad area of applications. This section will present immune-based systems specially designed to solve constrained, multi-modal and combinatorial optimization problems.

4.1 Constrained Optimization

Hajela & Lee (1996), Hajela *et al.* (1997) and Hajela & Yoo (1999), described the implementation of a constrained genetic search to simulate the mechanics of a biological immune system. The authors argued that the immune system capabilities of performing schema (pattern) recognition and adaptation could be used advantageously to improve the performance of genetic algorithms in structural optimization problems. Their work focused on two aspects: using the immune system capabilities to enhance the convergence of a GA approach, and handling the design of constraints in the GA based optimization. Their approach was applied to the problem of optimally designing a 10-bar truss structure for minimum weight and with pre-defined allowable constraints on maximum stresses of tension and compression in the bar elements (see Figure 4(a) for an illustration).

Like the majority of GA applications, they used a binary encoding for the strings representing the immune components (antigens and antibodies). The fitness of an individual was determined by its ability to recognize either a specific or a broad group of antigens, given by a function that measured the number of matching bits between a pair of strings: $Z = \sum t_i$, where $t_i = 1$ if there was a match in the i-th location of the two strings, and 0 otherwise. The process of handling constraints in their algorithm is depicted in Figure 4(b).



(a) (b)

Figure 4: (a) Example of structural optimization problem studied. (b) Constraint elimination using immune principles.

The chromosomal makeup of the feasible designs was selected as the antigens to which the antibodies had to be evolved. There was a co-adaptation of the unfeasible design representations to the structure of feasible designs, reducing constraint violations in the population. In this process, GA simulations were performed using unconstrained scalar functions to define the fitness.

4.2 Multi-Modal Optimization

Fukuda *et al.* (1999) proposed an immune algorithm that modeled mathematically the immune *diversity*, *network theory* and *clonal selection* as a multi-modal function optimization problem. The index of diversity and multiple solution vectors introduced were kept as memory of the system. The parallel between the immune system and algorithm is depicted in Table 3.

The algorithm could be realized in six steps according to Figure 5. The authors pointed out as the main characteristics of their method the diversity among the many candidate solutions and an efficient parallel search. Equations (5) and (6) determine affinities $ay_{v,w}$ and ax_v between two antibodies v and w, and an antibody v and an antigen, respectively

$$ay_{v,w} = \frac{1}{1+H}, \tag{5}$$

$$ax_v = opt_v, \tag{6}$$

where opt_v corresponds to the evaluated value to show the connectedness between antigen and antibody v. $H_j(N)$ is a parameter related to the informative entropy of locus j in the lymphocyte population

Table 3: Comparison between the immune algorithm and the immune system.

Immune System	Immune Algorithm
Antigen	Problem to be solved
Antibody	Best solution vector
Recognition of antigen	Identification of the problem
Production of antibody from memory cells	Recalling a past successful solution
Lymphocyte differentiation	Maintenance of good solutions (memory)
T-cell suppression	Elimination of surplus candidate solutions
Proliferation of antibody	Use of genetic operators to create new antibodies

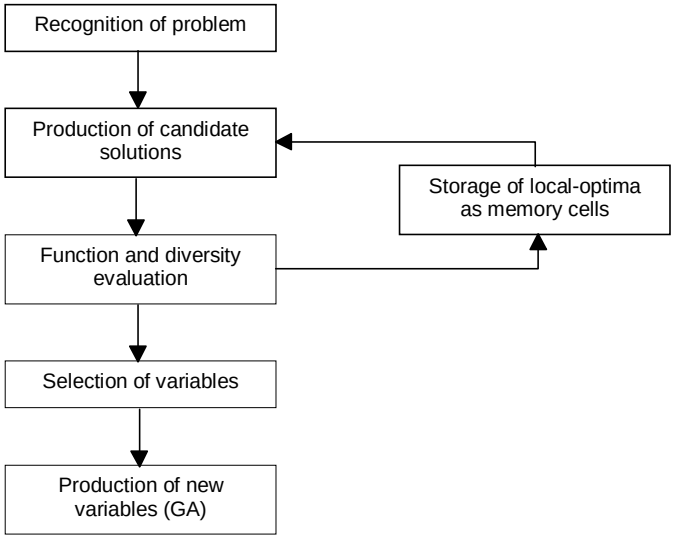
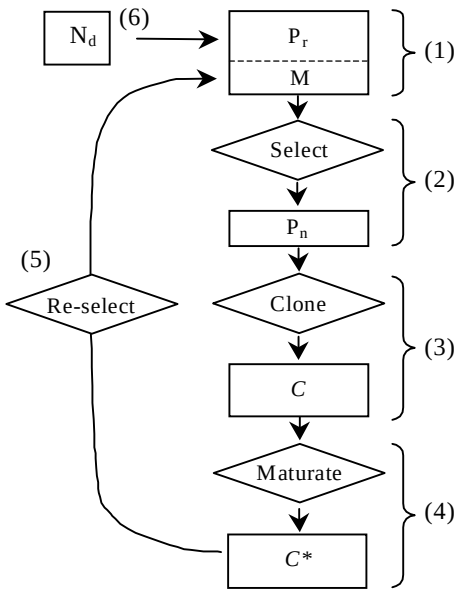


Figure 5: Flow chart of the immune algorithm.

$$H_j(N) = \sum_{i=1}^{S} - p_{i,j} \log p_{i,j},$$
$$H(N) = \frac{1}{M} \sum_{j=1}^{M} H_j(N), \tag{7}$$

where N is the size of the antibodies, S the variety of allele and $p_{i,j}$ the probability that locus j is allele i.

De Castro & Von Zuben (2000a) presented a *clonal selection algorithm*, which took into account the *affinity maturation* of the immune response, in order to solve complex problems, like learning and multi-modal optimization. Their algorithm constitutes an implementation of the biological processes and does not account for any mathematical sophistication to enhance its performance in particular tasks.



(a)

(1) Generate a set (P) of candidate solutions, composed of the subset of memory cells (M) added to the remaining (P_r) population ($P = P_r + M$);
(2) Determine (Select) the n best individuals of the population (P_n), based on an affinity measure;
(3) Reproduce (Clone) these n best individuals of the population, giving rise to a temporary population of clones (*C*). The clone size is an increasing function of their affinity;
(4) Submit the population of clones to a hypermutation scheme, where the hypermutation is proportional to their affinity. A maturated antibody population is generated (*C**);
(5) Re-select the improved individuals from *C** to compose the memory set M. Some members of P can be replaced by other improved members of *C**;
(6) Replace d antibodies by novel ones (diversity introduction). The lower affinity cells have higher probabilities of being replaced.

(b)

Figure 6: The clonal selection algorithm. (a) Block diagram. (b) Step-by-step procedure.

The main features of the clonal selection theory they modeled were:

- generation of new random genetic changes, subsequently expressed as diverse antibody patterns by a form of accelerated somatic mutation;
- phenotypic restriction and retention of one pattern to one differentiated cell (clone);
- proliferation and differentiation on contact of cells with antigens.

Their algorithm runs in six steps, according to Figure 6(a) and (b). This strategy was applied to a simple instance of the travelling salesman problem, a binary character recognition task and a multi-modal function optimization problem.

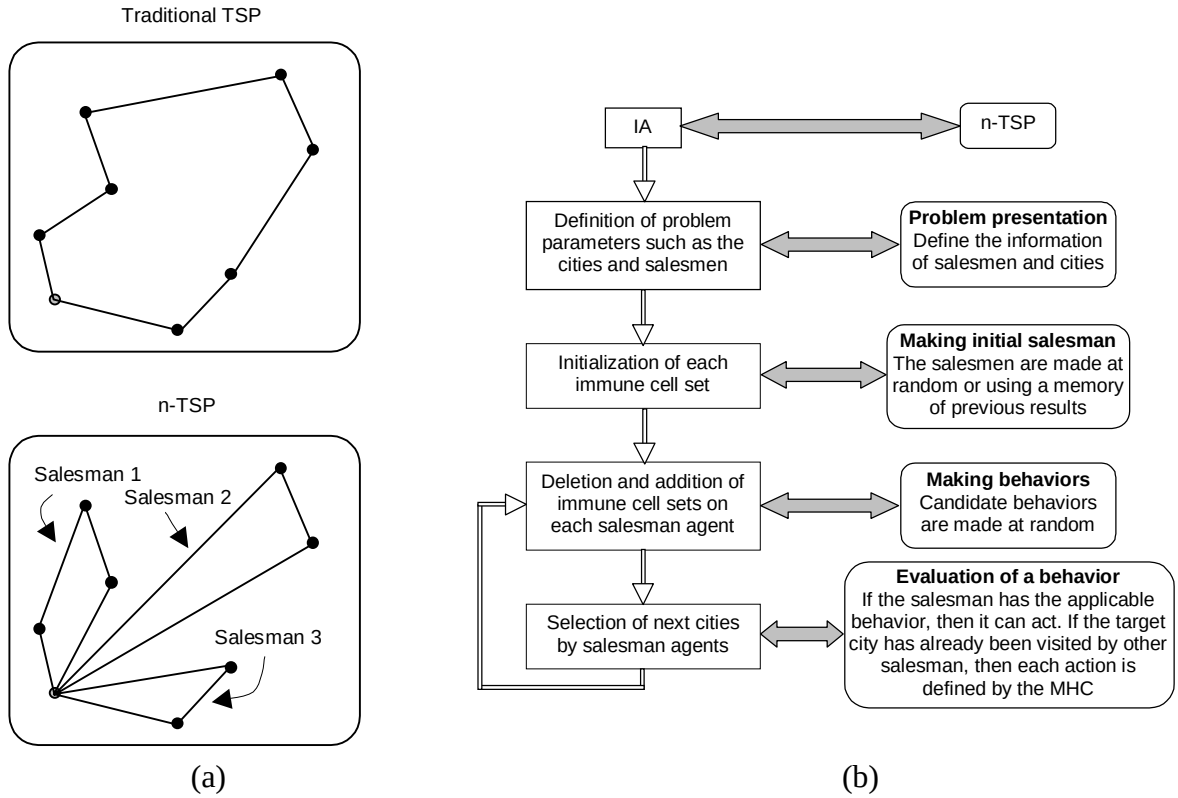
4.3 Combinatorial Optimization (n-TSP Problem)

The travelling salesman problem (TSP) is one of the most known and studied combinatorial optimization problems. Simply stated, the travelling salesman must visit every city in his territory exactly once and then return to the starting city. The question is: given the cost of travel between all cities, which is the tour with smallest cost? For sake of simplicity, the reader must consider as cost, basically the length of the itinerary traveled by the salesman. The n-th agents TSP (n-TSP) is an extension of the traditional TSP problem, where n salesmen are available for finding the minimal tour. The salesmen might perform independent routes and start from the same base city. Figure 7(a) depicts the relationship between the traditional TSP and the n-TSP problem.

Endo *et al*. (1998) and Toma *et al.* (1999) proposed an adaptive optimization algorithm based on the *immune network* model and *MHC peptide presentation*. In this model, immune network principles were used to produce adaptive behaviors of agents and MHC was used to induce competitive behaviors among agents. The agents possessed a sensor, mimicking MHC peptide presentation by macrophages, the T-cells were used to control the behavior of agents and the B-cells were used to produce behaviors. Table 4 summarizes the relationship between the n-TSP problem and the immune system. The algorithm was specially designed to solve the n-TSP problem, and its relation with it is illustrated in Figure 7(b).

Table 4: Immune cells and molecules and their roles in the n-TSP problem solving.

Immune System	Role in the n-TSP problem
Antigen	Contains information about the cities and salesmen
Macrophage	Selects the city number that the salesman agent must visit
T-cells	Help the activation of B-cell
B-cells	Produce antibodies
Antibody	Perform the behavior of an agent



(a) (b)

Figure 7: (a) n-TSP agents. (b) Proposed immune algorithm (IA) for solving the n-TSP problem. Each immune cell set is composed of three kinds of cells, called a macrophage, a B and a T-cell.

The system operated as follows: first macrophages acquired a city number at random and presented it to the T and B-cells. If a T-cell recognized this number, it tried to help B-cells. If T and B-cells recognized the same number, the B-cell produced an antibody and traveled. Then MHC was changed.

5. Neural Network Approaches

Artificial Neural Networks (ANN) are computational tools originally designed to model the human brain aiming at producing an "intelligent behavior". Several similarities and differences between the nervous system and the immune network theory have been identified, suggesting that one field of research might have much to gain from one another. This section will start depicting the points in common and disagreements between the two approaches. A few neural network and hybrid models will also be presented.

5.1 Similarities and Differences

The nervous system is commonly decomposed into sensory and motor parts. An analogous separation into recognition and effector functions can be made in the immune system, where effector mechanisms lead to the elimination of the antigens. In neural systems, assimilation of memories appears to be achieved by alteration of the strengths of connections between neurons, rather than changes within the neurons themselves. Further, the brain allows memories to be addressable by content, so that the frequent death of individual neurons does not drastically affect the performance of the brain as a whole. The immune system possess a *cross-reactive memory* that is observed when an individual develops a memory to one antigen and is challenged with a related, but different one (Hoffmann, 1986; Ada & Nossal, 1987; Smith *et al.*, 1997). The cross-reactive memory, *clonal expansion* and *programmed cell death* rates allow the immune system to dynamically allocate resources as needed in a distributed environment (Dasgupta, 1999a).

Some important common features, as basic cognitive mechanisms, shared by the neural networks and the immune system, are of great interest, and can be described as follows (Jerne, 1974; Hoffmann, 1986; Hoffman *et al.*, 1986; Vertosick & Kelly, 1989, 1991; Dasgupta, 1997, 1999a):

- both systems consist of an enormous number and diversity of cells. In humans, the immune system consists of roughly 10^{12} lymphocytes (B and T cells), and the central nervous system consists of about 10^{10} neurons.

- the individual cells are highly specialized in their functions and present great diversity of receptors.
- the immune system recognizes and responds to complementary shapes of a great variety of large molecules. The nervous system recognizes and responds to different kinds of patterns, like visual, auditory and sensory stimuli.
- the synaptic strengths between neurons can be excitatory (stimulating) or inhibitory (depressing), giving rise to many different activity patterns. The inter-lymphocyte interactions via cell-cell contact, or via chemical mediators have varying strengths which can be helping or suppressing.
- both systems exhibit memory, early impressions leave a particularly deep and lasting imprint into the network. Patterns of synaptic strengths constitute a memory that is auto-associative and non-hereditary. Some activated lymphocytes become special memory cells that are content-addressable, and non-hereditary.
- in the nervous system, a combination of global/local learning rules occurs, while changes in lymphocyte concentration constitute the mechanisms for learning within the immune system.
- definite recognition can be achieved with a threshold affinity. The immune and nervous systems share this property.

5.2 A Growing Boolean Competitive Network

De Castro & Von Zuben (2000b) developed a growing Boolean competitive network based on the *clonal selection* principle and some cognitive characteristics of the immune system. The main features of the proposed algorithm are: competitive learning, automatic generation of the network architecture and binary representation of the connection strengths (weights).

Figure 8(a) depicts the overall steps of their algorithm. The main loop of the competitive strategy can be summarized as follows:

1. choose an antigen (input pattern) **Ag** according to its probability density distribution P(**Ag**).
2. determine the highest affinity cell k, according to Equation (8).
3. update the weight vector $\mathbf{w}_k$ of the most stimulated cell.
4. increment the concentration level τ_j for the selected cell ($j = k$).
5. label the cell k with highest affinity with input $\mathbf{Ag}_a$, and attribute $v_a = k$.

$$k = \arg\max_k \left\| \mathbf{Ag} - \mathbf{Ab}_k \right\| . \tag{8}$$

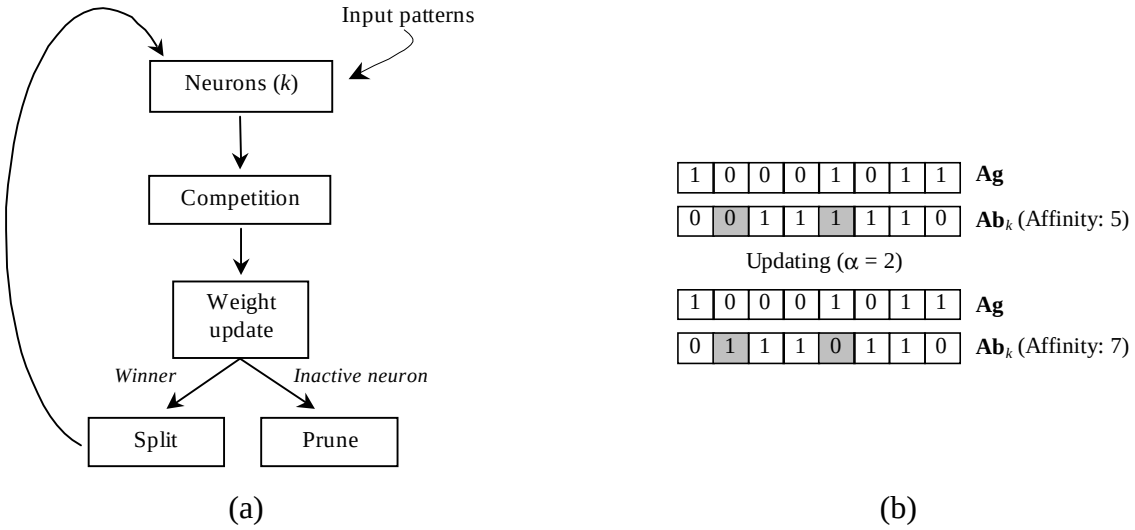


Figure 8: ABNET. (a) Main steps of the learning algorithm. (b) Weights updating procedure.

The weights updating is a guided search, such that the weights become a more perfect complement of the antigens, and is similar to a multi-point mutation usually employed in evolutionary search algorithms (see Figure 8(b)). α is called the hypermutation rate and is directly related to the capability of performing the affinity maturation of a given antibody.

This network was successfully applied to several problems, such as binary character recognition, major logic decision and pattern classification.

5.3 Associative Memory

An associative memory can be seen as an irregular hypersurface in a space containing valleys, corresponding to memorized patterns. The local minima of the function that describe this surface are called attractors, which represent the stored patterns.

Abbattista *et al.* (1996) presented an associative memory model for storing and retrieving noisy patterns based on the *immune network theory*. They tried to increase the memory capacity and retrieval performance, of a variation of the discrete Hopfield network (Hopfield, 1984) by exploring the *recruitment mechanism* of the immune network. This mechanism was used to define a population of points on an L-dimensional space representing a hypersurface. The best points of this population were taken as the attractors. Like in the discrete Hopfield network case, this algorithm is composed of a learning (storing) phase and a recall phase.

Their algorithm was applied to a bipolar dataset in which the affinities were measured via the Hamming distance between individuals. Some results were presented with relation to the storage capacity of their model, and its performance compared to the Hopfield network for a single example, demonstrating a superior error-correction capability of their model.

5.4 An Unorthodox Neural Network

Hoffmann (1986) and Hoffmann *et al.* (1986) used the analogy between the *immune system network theory* and the *central nervous system network* to formulate an unorthodox neural network model.

The immune system was viewed, in their network theory, as an *N*-dimensional system containing a very large number of singular points representing attractors. Learning in this system corresponded to transitions to stable steady states with higher "survival" values. The strength of interaction between any two clones remained fixed. This was in contrast to the traditional view of learning in the central nervous system, according to which the process involves changes in the strengths of synaptic connections between neurons. This led to the denomination "unorthodox neural network". Figure 9 illustrates the basic features of their network learning algorithm. Table 5 summarizes the relationship between their neural network model and the biological immune system properties.

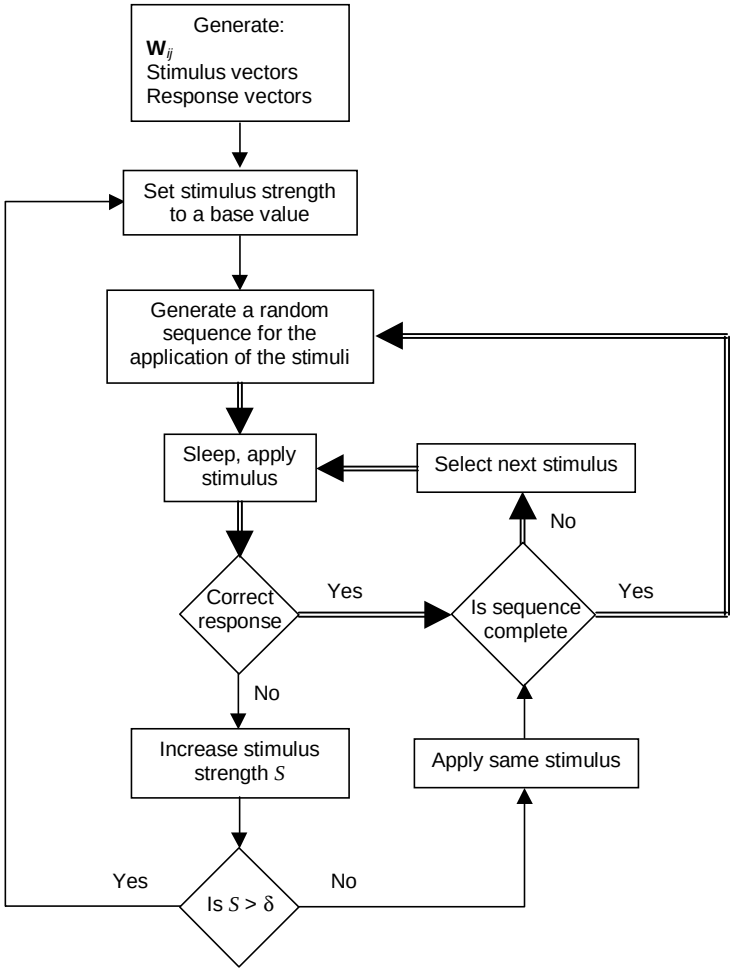


Figure 9: Basic features of the network supervised learning algorithm without changing the synaptic connection strengths ($\mathbf{W}_{ij}$). When a set of stimuli has been learnt, the system remains in the cycle shown in double line arrows. δ is a predefined threshold.

Table 5: Relationship between the biological immune system and the proposed neural network model.

Immune System	Neural Network Model
Clone	Neuron
Size of a clone	Rate of firing a neuron
Number of clones	Number of neurons
Stimulation/suppression of a clone	Stimulation/suppression of a neuron
Stable steady states (long-term immunity)	Singular points (attractors)

5.5 A Multi-Epitope Approach

The works of Vertosick & Kelly (1989, 1991) conjectured that the immune system might represent an alternative paradigm in which to search for neural network architectures. Based on the Parallel Distributed Processing (PDP) theory (Rumelhart *et al.*, 1986), they tried to map the *immune network theory* into a PDP immune network.

It was argued that B lymphocytes (or lymphocyte clones), could act as the units that compose a PDP network, in the sense that they receive inputs (from APCs, antigens and/or cytokines), generate output (antibody), remember antigenic specificity and convert inputs (antigenic stimulation) into output (antibody secretion) in a quantitative fashion. The PDP immune network architecture could be multi-layered, where lymphocytes would correspond to input units, plasma cells would be output units, and lymphocytes producing anti-idiotypic antibodies would serve as examples of hidden units. The definition of the connection weights within the immune network would depend upon the definition of the units. The connection weights between two lymphocytes could be defined in terms of the affinities between their immune receptors. However, if the units were defined as clones, then both the affinity and the relative sizes of two clones would have to be considered in the definition of the weight between them. No learning rule was explicitly presented, though the authors strongly suggested that the learning behavior of the immune system uses an unsupervised, local learning rule.

Their model also included cytokines, which were responsible for the clonal expansion of the populations and subsequent alteration of the connection strengths of a PDP composed of clonal units. Another possible role of cytokines was related to the network temperature. The simulated annealing of a PDP network was used to find the lowest energy configuration of the network, by altering the shape of the activation functions of the units.

6. Anomaly Detection

The normal behavior of a system is often characterized by a series of observations over time. The problem of detecting novelties, or anomalies, can be viewed as finding deviations of a characteristic property in the system.

6.1 Computer Security

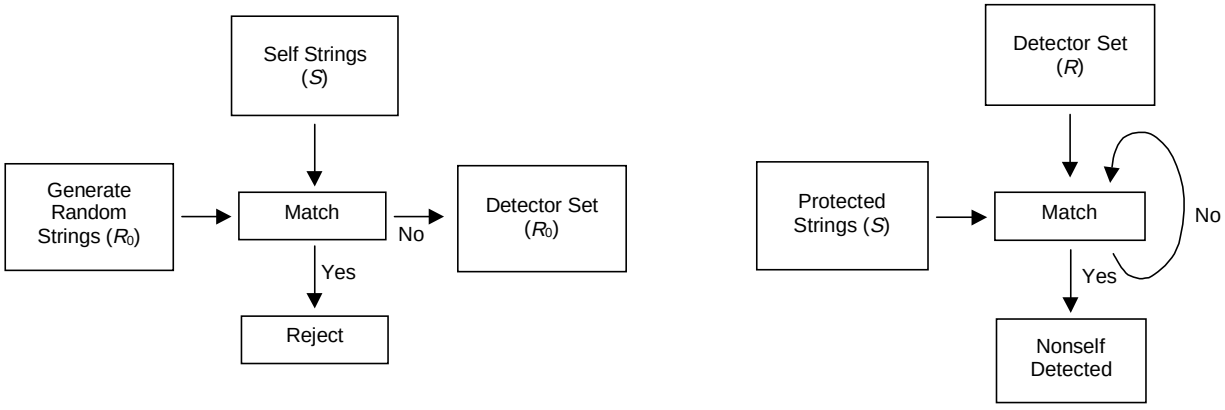
The problem of protecting computers from viruses, unauthorized users, etc., constitutes a rich field of research for anomaly (or change) detection systems. Forrest *et al.* (1994) compared the problem of protecting computer systems to that of learning to distinguish between *self* and *non-self*. They described a change-detection strategy based upon the *thymic negative selection* intrinsic to our immune system.

Their algorithm runs in two phases. In the first phase, a set of detectors is generated according to Figure 10(a) and, in the second phase, the protected data is monitored by comparing them with the generated detectors (see Figure 10(b)). If the number of contiguous bits in common between two strings is greater than or equal to *r*, then the strings are said to match each other. The authors also presented equations estimating the probability that a match occurred at at least *r*-contiguous positions between two random strings and the change-detection probability for different configurations of the system.

The main observations about this algorithm were:

1. its tunable with relation to the probability of detection;
2. the size of the detector does not necessarily grow with the number of strings being protected;
3. the probability of detection increases exponentially with the number of independent detection algorithms;
4. detection is symmetric; and
5. there is an exponential cost of generating detectors with relation to the size of the self set.

In order to overcome the main drawback of the above-mentioned strategy (item 5), D'haeseleer *et al.* (1996) proposed two novel detector-generating algorithms which run in linear time with respect to the size of the input. They also discussed how to set parameters for the algorithms, like repertoire sizes, probabilities of match and failure in detection, practical issues and rules of thumb for *r*-contiguous bit matching rules. The algorithms run in two phases and are based on dynamic programming. In the first algorithm a counting recurrence problem for the number of unmatched strings in *S* was solved.



(a) (b)

Figure 10: Anomaly detection algorithm. (a) Generation of valid detector set (censoring). (b) Monitoring of protected data.

The second phase was responsible for the generation of strings unmatched by *S*. The second algorithm possessed the same second phase as the first one, with the difference that it tried to select the detectors placing them as far apart as possible, aiming at achieving a better coverage of the string space with the same number of detectors.

6.2 DNA-Based Negative Selection

DNA computation is based upon hydrogen bonding based matchings, called hybridizations, between Watson-Crick complementary pairs, A-T (Adenine-Thymine) or C-G (Cytosine-Guanine). A single strand (an oligonucleotide) will bind other oligonucleotides that match most closely its sequence under the operation of Watson-Crick complementation.

Deaton *et al.* (1997) reduced the *change detection algorithm* of Forrest *et al*. (1994) (briefly discussed in the previous section), to the problem of detecting changes in strings. In their DNA implementation, template matching hybridization reactions between DNA oligos were used to detect change.

The censoring and monitoring algorithms presented in Figure 10 were studied with techniques from molecular biology. Figure 11 depicts the DNA based negative selection algorithm. For details concerning DNA computation, refer to Adleman (1994).

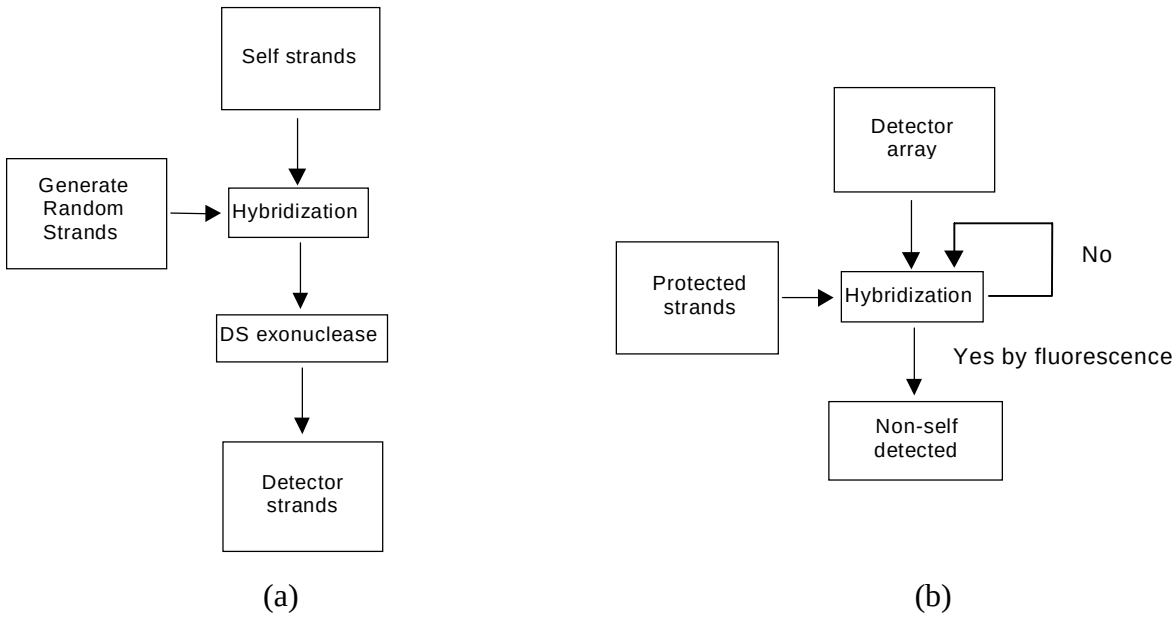


Figure 11: DNA implementation. (a) Censoring. (b) Monitoring.

6.3 Virus Detection and Elimination

In the system developed by Kephart (1994), a set of antibodies to previously not encountered computer viruses or worms (agents) was generated so as to promote a faster and stronger response to future infecting agents. He was also concerned about minimizing the risk of an autoimmune response, in which the computer immune system would mistakenly identify legitimate software as being undesirable.

A particular virus was recognized via an exact or fuzzy match to a relatively short sequence of bytes occurring in the virus (called a “signature”). The process by which the proposed computer immune system established whether new software contained a virus had several stages. Integrity monitors, which used checksums to check for any changes to programs and data files, had a notion of *self* that was: any differences between the original and current versions of any file were flagged, as were any new program. However, evidence of a *non-self* entity was not by itself enough to trigger a *computer immune response*. Mechanisms that employed the complementary strategy of “knowing the enemies” were also brought into play.

The capture of a virus sample by *decoy programs* (kept at different strategic areas in memory) was somewhat analogous to the ingestion of antigen by *antigen presenting cells*. In the computer immune system, the infected decoys were then processed by another component of the immune system, called a signature extractor, so as to develop a recognizer for the virus.

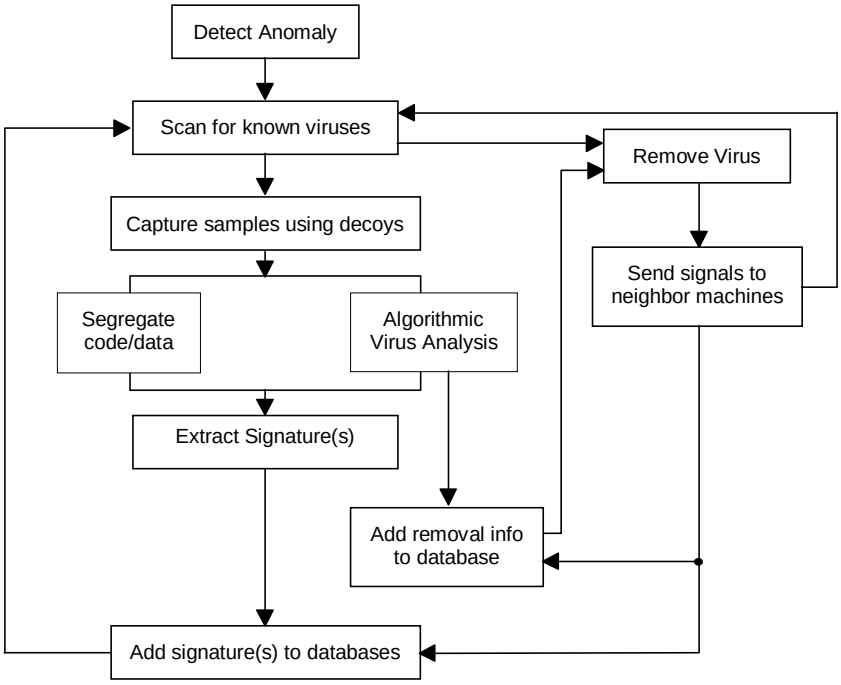


Figure 12: Main components of the computer immune system and their relationship.

The computer immune system had an additional task that was not shared by its biological analog: it had to attempt to extract from the decoys information about how the virus attached to its host, so that infected hosts could be repaired (if possible). Hence, the system automatically developed both a recognizer and a repair algorithm appropriate to the virus.

Viral self-replication was dealt with self-replication, in the sense that, detection of a virus by a single computer could trigger a wave of *kill signals* that propagated along the path taken by the virus, destroying the virus in its wake. Figure 12 depicts the main components and their respective function within the immune system discussed in the present section.

Other sources of reference from the same author concerning computer virus detection and elimination can be found in Kephart *et al.* (1997, 1999).

6.4 Image Inspection System

Aisu & Muzutani (1996) proposed an immunological learning system aiming at integrating the distributed search of new agents and constraint relaxation among them. Their work was based on those of Farmer *et al.* (1986), Forrest *et al.* (1994) and D'haeseleer *et al.* (1996). They applied *immune network dynamics*, based upon a dynamic equation, to study the interactions among antibodies and between antibodies and antigens. The dynamic equation took into account the stimulation and suppression among antibodies, their stimulation by antigens and a natural death rate (see Equation (9)).

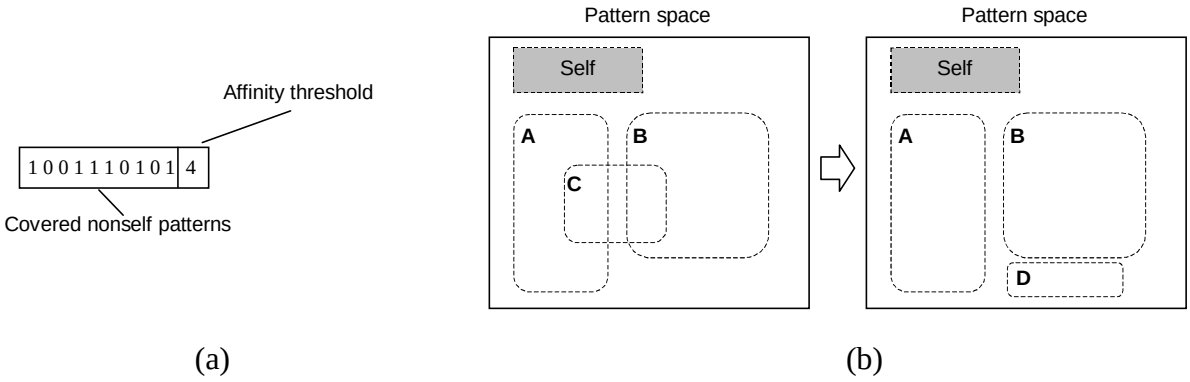


Figure 13: (a) Genetic encoding for the detectors. (b) Suppression of detector **C** that (partially) covers the same portion of the pattern space. A new detector **D** is created.

Their system consisted of distributed antibodies, named detectors, which reacted to non-self patterns. Each detector was an independent agent doing checks in parallel, with the limited role of detecting their assigned non-self patterns. They used a Hamming shape-space to study cell-cell interactions, but their detectors (antibodies) contained the affinity threshold embodied in the last position (allele) of the string. The combination of a diversity generation mechanism and suppression resulted in redundancy avoidance among the coverage of each detector. Figure 13(a) depicts their encoding scheme and Figure 13(b) represents how the suppression term of Equation (9) can assist in the problem of eliminating detectors that cover the same portion of the pattern (antigen) space.

The algorithm works as follows:

- generate an initial set of detectors;
- generate a new detector randomly or by using mutation and add it to the detectors set;
- evaluate the detectors, eliminating those self-recognizing ones;
- renew the concentration of detectors using the dynamic equation given by (9);
- delete detectors with concentration level bellow a given threshold.

$$\dot{x}_i = c\left(\sum_{j=1}^{N} m_{j,i} x_i x_j - K_1 \sum_{j=1}^{N} m_{i,j} x_i x_j + \sum_{j=1}^{N} m'_{j,i} x_i y_j\right) - K_2 x_i \,. \tag{9}$$

The first term represents the stimulation of antibody *i* by other antibodies, the second term represents the suppression of antibody *i* when it is recognized by other antibodies. The third term corresponds to the antigenic stimulation of **Ab** *i*, and the fourth term is the natural death rate.

6.5 Image Segmentation

The pattern recognition task performed by the immune system has much in common with the aerial image segmentation problem. This was studied by McCoy & Devarajan (1997), who used a

negative selection algorithm to construct a set of detectors that weeds out everything but the desired class.

Their algorithm assumed a discrete feature space represented by an *L*-digit bit string generated from images extracted from single band infrared-sensors of road pixels. A string *m* = <0...010...0> contains a digit 1 (in position *k*) indicating the region of feature space for the target pattern. The detectors were produced according to the rule: generate random binary strings, if position *k* is 0, add the string to the population. If the logical OR of the population constitutes the exact complement of *m*, stop. This procedure generates the non-self detectors set, and if none of the population has any bit in common with the test string, then it belongs to the target class.

The authors compared the results achieved by their artificial immune system and those obtained by genetic programming, concluding that both methods are suitable for parallel implementation but the new one is expected to adapt more readily to changes in its sample data, being dynamically adjustable. They also argued that finding a population of detectors that covers non-self features is easier than finding a single optimal detector, since there are many ways to arrive at an acceptable solution.

6.6 Novelty Detection in Time Series Data

Dasgupta & Forrest (1996) proposed a novelty detection algorithm for time series data, based on the previously discussed *negative-selection algorithm* introduced by Forrest *et al.* (1994) and D'haeseleer *et al.* (1996).

Their algorithm can be summarized as follows:

- collect sufficient time series data to exhibit the normal behavior of a system;
- determine the range of variation of data and perform a binary encoding according to the desired precision;
- select a suitable window (concatenation of a fixed number of data points) size which captures the regularities of interest;
- slide the window along the time series, in non-overlapping steps, and store the encoded string for each window as *self*, from which detectors will be generated;
- generate a set of detectors that do not match any of the self strings;
- once a unique set of detectors is generated from the normal database of patterns, it can probabilistically detect any change (or abnormality) in patterns of unseen data;
- while monitoring the system, use the same encoding scheme for the new data patterns. If a detector is activated, a change in behavior has occurred and an alarm might signal.

The authors reported results for two data sets: a simulated cutting dynamics of a milling operation and a synthetic signal. They observed that the number of *r*-contiguous bits chosen by the matching function was responsible for tuning the reliability of detection against the risk of false positives. In a later work (Dasgupta & Forrest, 1999), the authors presented a more detailed discussion about the same artificial immune system.

7. Agent-Based Approaches

An agent is anything that can be viewed as perceiving its environment through sensors and acting upon that environment through effectors. The immune system is composed of an enormous set of cells, molecules and organs, which can be viewed as immune agents distributed all over our bodies.

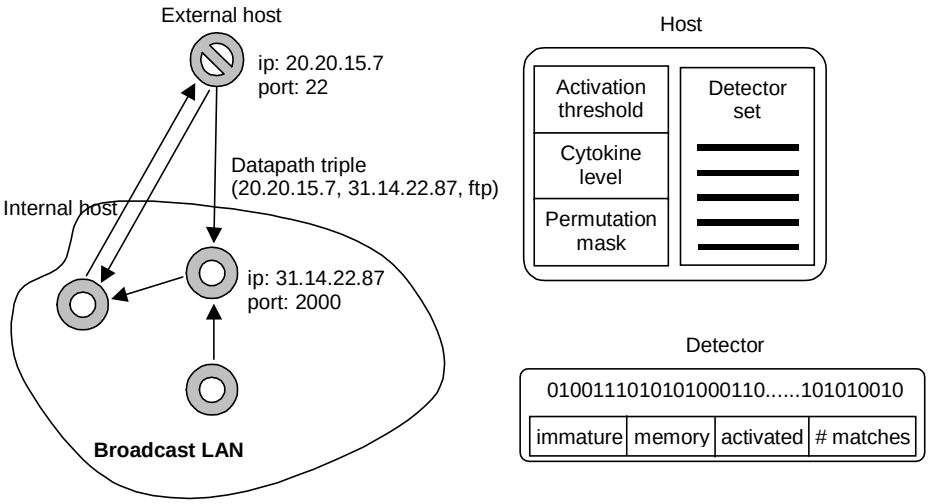
7.1 Network Security

Forrest *et al.* (1997) and Hofmeyr & Forrest (1999, 2000) have been pursuing the problem of developing an artificial immune system that is distributed, robust, dynamic, diverse and adaptive, with applications to computer network security.

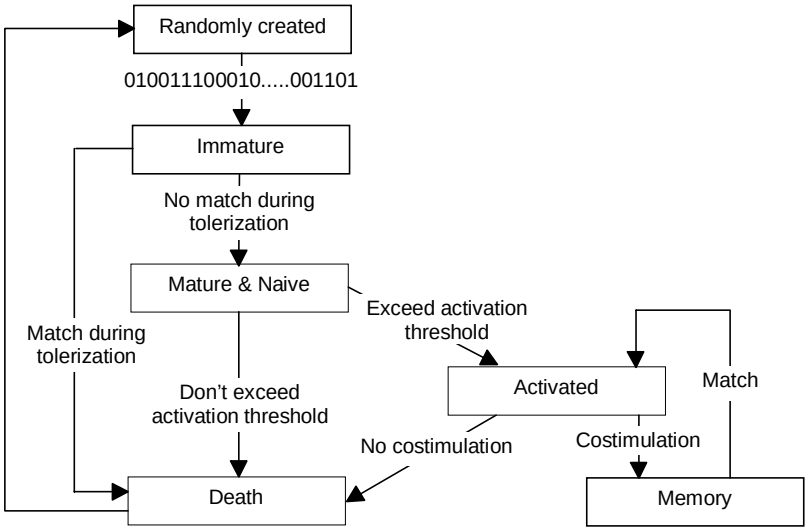
In their system, the several immune system cells and molecules were simplified by the definition of a basic type of detector that combined useful properties from these elements. The detector cell had several different possible states, roughly corresponding to thymocytes, naive B-lymphocytes and memory B-lymphocytes. The detectors were represented by bit strings of a given length, and a small amount of state, as depicted in Figure 14(a). Detection was performed by a string match process that took into account the number of *r*-contiguous bits between two strings. The definition of *self* (tolerization period) was performed by the negative selection algorithm described in Forrest *et al.* (1994). The maturation of naive detectors into memory detectors, together with the negative selection, were responsible for the learning part of the system (see Figure 14(b)). The authors used permutation masks to achieve diversity of detectors.

The authors reported results of a computer network intrusion-detection application, but suggested that this artificial immune system can be successfully applied to other classes of networks, including social nets, organizations, networks of markets and neurological or ecological networks.

Based on these works and those described in Section 7.1, Kim & Bentley (1999a,b) are working on the development of a network intrusion detection system inspired in the immune system.



(a)



(b)

Figure 14: (a) Architecture of the AIS for computer network security. (b) Life cycle of a detector.

In Kim & Bentley (1999a), the authors reviewed and assessed the analogy between the human immune system and network intrusion detection systems. They aimed at unraveling the significant features of the IS that would be successfully applied to the task of detecting intrusions in computer networks. Upon their analysis, they identified three fundamental requirements for the derivation of the design goals for network-based intrusion detection, named *distribution*, *self-organization* and *being lightweight*. Table 6 describes the immune system components and functions that satisfy the three requirements listed.

Table 6: Components of the immune system that satisfy the requirements for the development of an efficient intrusion detection system (IDS).

Characteristic of an IDS	**Immune System**
Distribution	Immune network
	Unique antibody sets
Self-Organization	Gene library evolution
	Negative selection
	Clonal selection
Lightweight	Approximate binding
	Memory cells
	Gene expression

Table 7: Relationship between the network intrusion detection system and the immune system.

Network Environment	**Immune System**
Primary IDS	Bone marrow and thymus
Local hosts	Secondary lymph nodes
Detectors	Antibodies
Network intrusions	Antigens
Normal activities	Self
Abnormal activities	Non-Self

In a further work (Kim & Bentley, 1999b), the authors proposed a Negative Selection Algorithm (NSA) with niching for network intrusion detection. They also suggested that an overall artificial immune model for network intrusion detection would be comprised by three distinct evolutionary stages: 1) negative selection, 2) clonal selection and 3) gene library evolution. Table 7 shows how they related the immune system with their network environment, and Figure 15 presents the physical architecture of their system (IDS corresponds to Intrusion Detection System).

The negative selection algorithm with niching simply replaces the random generation of detectors by the evolution of detectors towards non-self. In phase 1), the modified NSA was used to build self profiles, which were encoded in an appropriate data representation. In phase 2), the NSA with niching started generating detectors. After that, new self profiles were built by parsing newly captured network packets. In the third phase, the detector patterns in each detector set were compared to the patterns in each corresponding new self profiles. If the similarity between any detector pattern and new self pattern is above a pre-defined threshold, an alarm signal is given.

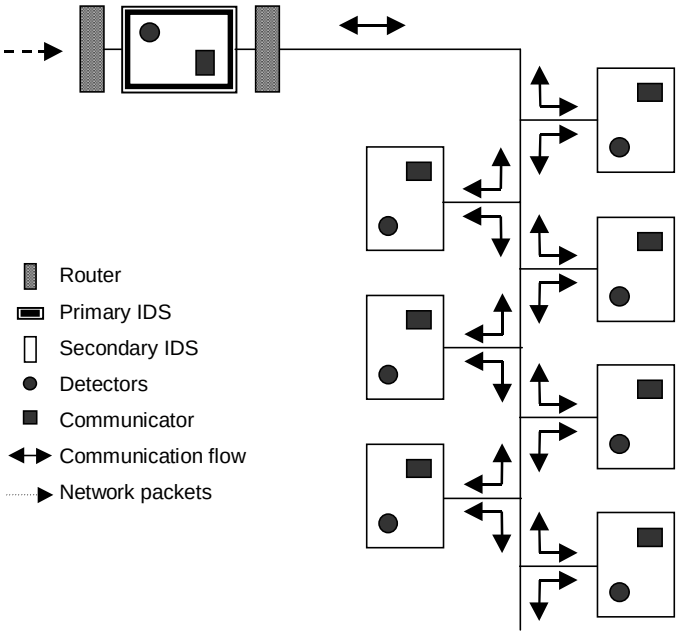


Figure 15: Physical architecture of an artificial immune system for network intrusion detection.

In a recent work, Dasgupta (1999b) proposed an agent-based system for intrusion/anomaly detection and response in networked computers. In his approach, the immunity-based agents roamed around the nodes and routers monitoring the situation of the network. The most appealing properties of this system were: mobility, adaptability and collaboration. The immune agents were able to interact freely and dynamically with the environment and each other.

Figure 16 depicts the types of agents employed and their hierarchical coordination. The decision/action agents could assume the forms of *helper*, *killer* or *suppressor* agents, like in the case of T-cells. The communicating agents corresponded to *lymphokines*, secreted by T-cells to regulate the immune response. Some of the monitoring agents worked in the complement space for monitoring changes (*non-self*), while others had the knowledge of known intrusions.

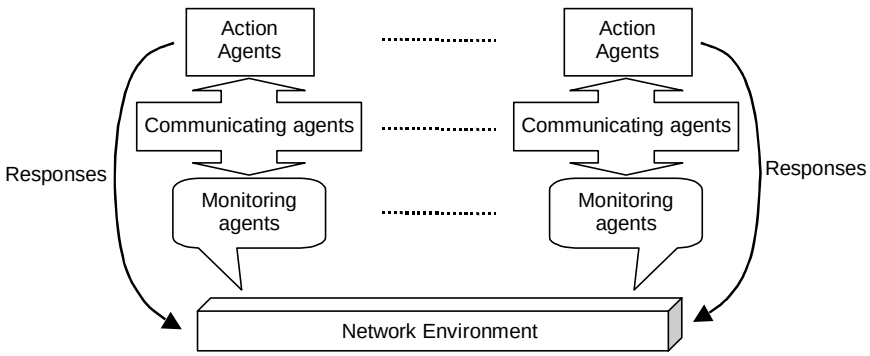


Figure 16: Conceptual view of the proposed multi-agent intrusion detection system.

7.2 Computer Virus Detection and Elimination

Okamoto & Ishida (1999a,b) proposed a distributed approach to computer virus detection and neutralization by autonomous and heterogeneous agents. This system detected viruses by matching a *self* information (like the first few bytes of the head of a file, the file size and path, etc.) against the current host files. Viruses were neutralized by overwriting the self information on the infected files and the recovering was attained by copying the same file from other uninfected hosts through computer network. Figure 17 depicts the whole anti-virus system and the virus neutralization mechanism.

Their system was composed of the following types of agents:

- *detection/neutralization agents*, named *antibody agents*;
- *killer agents* (mimicking *killer T-cells*) responsible for removing the altered files that were neutralized by antibody agents;
- *copy agents* that sent and received requests for copying uninfected files over the computer network; and
- *control agents* (mimicking *helper T-cells*) responsible for controlling the process of the anti-virus system.

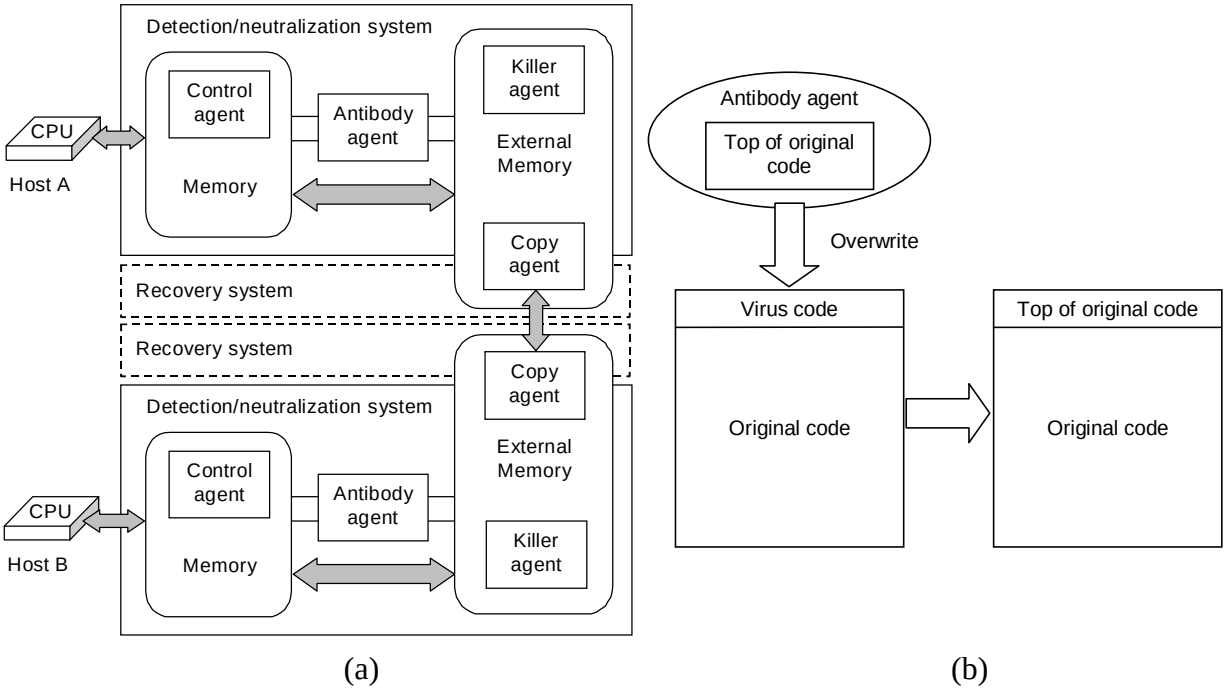


Figure 17: (a) Diagram of the anti-virus system. (b) Virus neutralization by antibody agent.

According to the authors, the main drawbacks of their approach were the critical determination of the size of the head part to be used by the antibody agent (a too long head could be very memory consuming, while a too small one could be ineffective), and the recovery through the network, that could cause deadlock or secondary infection.

7.3 Intelligent Buildings

The principle of building an automation system is to regard each device of this system as an information processing unit, and to execute control actions by transmitting messages among them. A set of microprocessors is used to transform the devices into information processing units. The term *intelligent buildings*, or *smart buildings*, is being used to describe *automated buildings*, where technology is used to realize rather complex functions, like water, gas and energy management, security, remote control, transportation and communication (within the building and with the outside world).

Dilger (1996) proposed an agent-based security system for intelligent home technology aiming at improving the technical facilities of a home. The security system was modeled similarly to the natural immune system in two ways: it was self-organized and capable of producing a flexible reaction according to the degree of danger. The sensors and actuators of the house were regarded as stationary agents simply defined based on states and rules. An interesting point of this security system was the fact that not only the presence of a burglar was detected by the sensors, but also outside events, like thunderstorms, etc.

The agents were defined according to the following syntactical scheme:

- device <name of the device type, e.g. motion detector, alarm, etc.>
- type <class of device>
- parameters <list of parameters that could be manipulated by the device>
- constants <list of constants>
- variables <list of local variables>
- $state_1,\ldots,state_n$

A state had the following form:

- status <value of the state>
- list of rules

In a later work, Dilger (1997) proposed the use of an evolutionary process to optimize the behavior of the system, i.e. to tune its relevant parameters. In addition, he pointed out several aspects of immune-based systems that were contained in the intelligent home, like self-definition and

maintenance. He regarded the situations (presence of burglars, weather, etc) as *antigens*, and the specifications of situations in the rules as *antibodies*, activated by certain antigens (situations). The Jerne *immune network* idea was brought up by the interconnection scheme of the agents composing the security system.

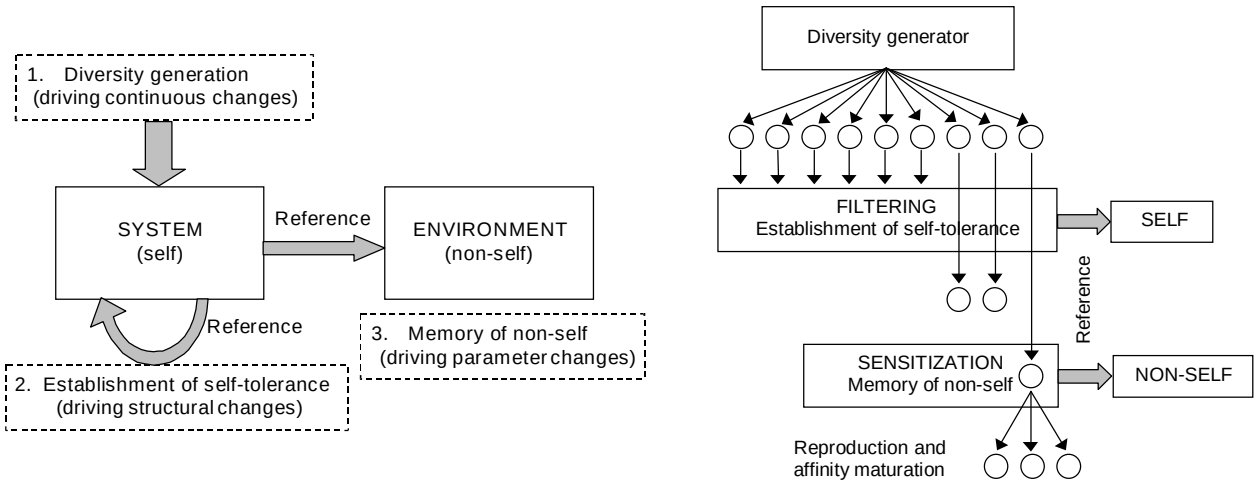
7.4 Adaptive Noise Neutralization

Based upon the immune properties of *diversity*, *self-tolerance* and *memory of non-self*, Ishida (1996c) developed an agent-based *immune algorithm* with possible applications to noise neutralization, group task achievement, model adjustment and decision making.

The author detached as one of the most striking characteristics of his algorithm its super adaptability, not only to a changing environment but also to a changing self (own system). The algorithm worked in three steps:

- *generation of diversity*;
- *establishment of self-tolerance*;
- *memory of non-self.*

Figure 18(a) presents a general outline of the algorithm. Figure 18(b) depicts a schematic diagram of the immune algorithm for an agent-based architecture. The author suggested an encoding scheme as those used by the traditional applications of a genetic algorithm.



(a) (b)

Figure 18: (a) Schematic diagram of the immune algorithm. (b) Immune algorithm for an agent-based architecture.

8. Learning

Learning is usually addressed to the processes of acquiring knowledge from experience and abstracting this knowledge to solve new, previously unseen problems. The process of immunizing (through vaccination, for example) is a clear example of an immune learning mechanism. Similar strategies can be used to solve problems like pattern recognition, concept learning, etc.

8.1 Pattern Recognition

Hunt & Cooke (1996) proposed a formal architecture for an artificial immune system (AIS) that was evaluated in pattern recognition problems. The key features of the immune system they explored were the *genetic mechanisms used to construct antibodies*, the *clonal selection* and *affinity maturation* of the immune response, the immune *content addressable memory*, the *matching mechanisms* of the immune system and its *network self-organizing properties*.

They used an object-oriented approach such that their algorithm was composed of a set of intercommunicating objects, like a bone marrow object, a network of B-cell objects and an antigen population. There was a main algorithm as illustrated in Figure 19(a). The most complex concept in their AIS was the B-cell object (see Figure 19(b)). The antibodies possessed a paratope representing the antigenic pattern they match and the antigens had a single epitope. The stimulation level of a B-cell object, given by Equation (10), took into account the strength of the match between an antibody and its neighbors (first term), its enmity for its neighbors (second term), the **Ag-Ab** affinity (third term), and the natural death rate (fourth term). k_i (i = 1,...,3) are constant values corresponding to possible inequalities between stimulation and suppression. A somatic hypermutation was used to increase the affinity between the B-cell objects and the antigens. The stimulation level and somatic hypermutation were determined based on a variation of the model proposed by Farmer *et al.* (1986).

$$stimulation = c\left[\sum_{j=1}^{N} m(a, xe_j) - k_1 \sum_{j=1}^{N} m(a, xp_j) + k_2 \sum_{j=1}^{n} m(a, y)\right] - k_3 \qquad (10)$$

As conclusions, the authors suggested that the proposed AIS has great potential for being applied to areas like classification, prediction, diagnosis and data mining.

The limitations and problems identified in this version of the ISYS system, led to the design of the JISYS system (Hunt *et al.*, 1999), which is a Java-based implementation of the ISYS system.

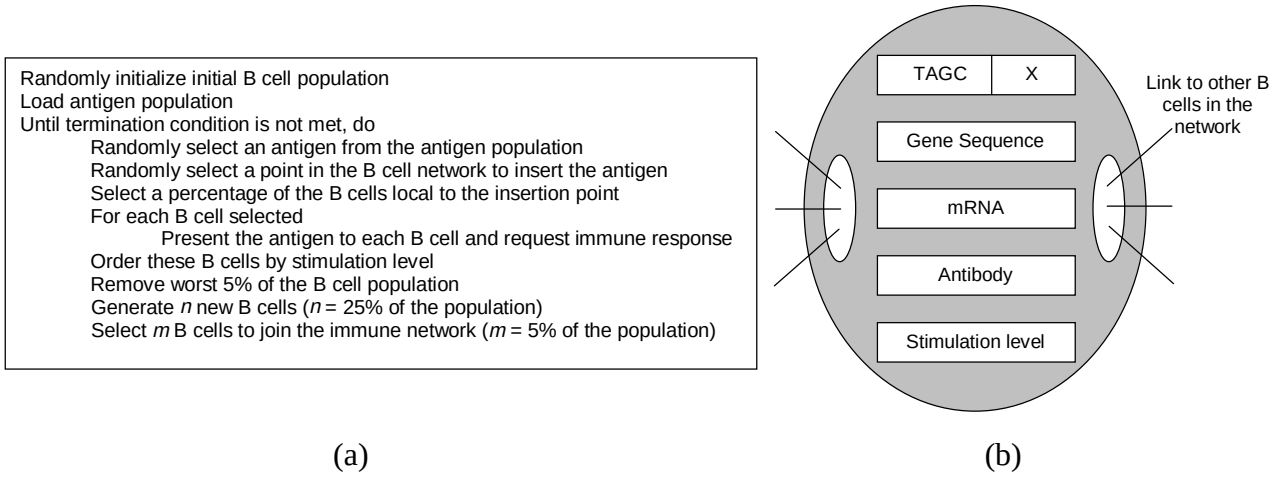


Figure 19: (a) The immune system object algorithm. (b) Structure of a B-cell object.

Table 8: Comparison of machine learning approaches. SO: Self-Organizing, U: Unsupervised, NTE: Negative Training Examples, OS/IN: One Shot/Incremental, SY: Symbolic, NT: Noise Tolerant, XOR: XOR problem.

Approach	**SO**	**U**	**NTE**	**OS/IN**	**SY**	**NT**	**XOR**
AIS	♦	♦	♦	O/I	♦	♦	
ANN		♦		O/I		♦	♦
LCS			♦	I	♦	♦	
MI			♦	O	♦		♦
CBR		♦	♦	O	♦	♦	

8.2 Concept Learning

Potter & De Jong (1998) used the *self/non-self discrimination* mechanism of the immune system as a source of inspiration for the development of a co-evolutionary genetic algorithm that differentiates examples from counter-examples of a given concept. Their model was limited to the interactions between B-cells and antigens, and was applied to concept learning from pre-classified positive and negative examples by equating them to foreign and self molecules, respectively. In the case of noise free examples, the system was evolved to a point where all the foreign and none of the self-molecules were recognized.

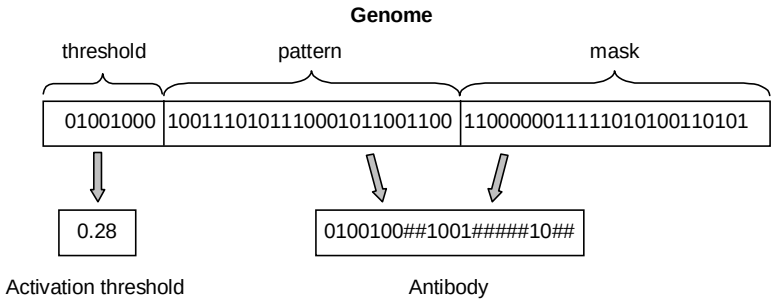


Figure 20: B-cell genotype to phenotypic mapping.

In this model, a B-cell consisted of an antibody type and a real-valued activation threshold that represented the binding strength required to initiate an immune response. The representation employed was based on the work of Forrest *et al.* (1993), where a binary *schema* represented an antibody and simple binary strings represented antigens. The matching function returned the percentage of matching bits between **Ag-Ab**, which was used to compute the binding strength. Figure 20 illustrates the genotype to phenotype mapping of B-cells. The antibody schema was produced from binary patterns and mask genes. A mask bit of '0' produced a "don't-care" schema value. The real-valued activation threshold was generated from an 8-bit threshold gene. A co-evolutionary genetic algorithm was used to evolve the B-cells such that individuals from multiple non-interbreeding species collaborated to solve a target problem. Each species (collection of B-cells having similar antibodies) represented only a partial solution. The fitness of a B-cell was determined by adding it to a "serum" composed of the current best B-cells. Foreign and self-molecules were then presented to the serum. If the **Ag-Ab** binding strength exceeded its activation threshold, then the antibody successfully recognized the antigen. The fitness of the B-cell was defined as the number of foreign molecules recognized by all the antibodies in the serum, minus the number of self-molecules flagged as foreign. The final solution consisted of the best B-cell from each species.

The results of this approach were compared to a sophisticated symbolic inductive learning system, called AQ, applied to a congressional voting record data set. The authors suggested that their strategy was capable of producing a more concise description of the concepts than the AQ method, with similar predictive accuracy, and argued that it happens due to the more flexible strategy employed by the co-evolutionary immune model.

8.3 The Baldwin Effect

The Baldwin effect proposes that learning or acquiring useful characteristics during a lifetime would cause succeeding generations to have higher probabilities of acquiring this same characteristics, even though the characteristics themselves are not genetically propagated.

Hightower *et al.* (1996) used a binary model of the immune system, together with the *clonal selection principle* and *affinity maturation* of the immune response to study the influence of learning in the evolution of the genetic representation of antibodies. Antibodies and antigens were simply represented as binary strings of same length and the match score given by the XOR operation (Hamming distance) taken between the two strings, i.e. the number of complementary bits. The binding value was a non-linear (sigmoidal) function of the match score (see Figure 21 for an illustration).

By varying the learning rate (somatic mutation rate), they showed the presence of the Baldwin effect, in the sense that learning accelerates evolution by allowing it to discover which individuals are nearest to the threshold of success. The authors suggested that the Baldwin effect disappeared when the non-linear binding function was replaced by a linear one.

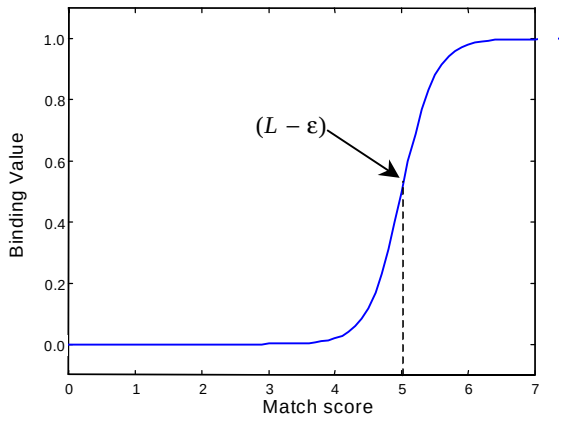


Figure 21: Non-linear relation between binding value and match score for a bit string of length $L = 7$ and affinity threshold $\varepsilon = 2$.

8.4 Generation of Emergent Properties

In order to study the generation of complexity shown in higher living organisms, Nagano & Yonezawa (1999) proposed a generative physical model constructed on complex systems based on a primitive immuno-defense system. The authors suggested that the origin of self-organization and ordered complexity are equivalent to the establishment of a “self system”, and hence can be

achieved by the generation of a self-recognition (*self/non-self discrimination*) mechanism and a punctuated equilibrium hypotheses.

The individuals of a non-self set were composed of DNA sequences and matched against an initial self-set of DNA sequences. Then, they were subjected to a genetic algorithm in order to observe the generation of complexity and the correlation among the DNA sequences and the self/non-self discrimination problem.

According to the authors, the most relevant results taken from their experiments were:

- the self/non-self recognition mechanism generated complexity and adaptability;
- due to the recognition mechanism, the self system was maintained regardless environmental fluctuations;
- each self system and population had properties of punctuated complexity and correlation; and
- each self system showed an adaptive behavior.

9. Inductive Problem Solving

Inductive learning, or inductive problem solving, is essentially a search problem. Slavov & Nikolaev (1998) and Nikolaev *et al.* (1999) introduced enhanced evolutionary strategies based on this new approach.

9.1 Finite-State Automaton

Slavov & Nikolaev (1998) proposed an evolutionary search algorithm based on a discrete version of a model of the *immune network dynamics*. The algorithm alternates continuously in cycles of three search phases, from oscillatory through asymptotic to chaotic, and the system self-regulates.

The authors applied their immune algorithm to solve an instance of the intractable finite-state automata induction problem (see Figure 22 for an illustration of a finite-state automaton subject of learning). Individual automata were associated with lymphocyte clones, the examples were assumed to be the antigens, and the fitness of the automaton was given by its concentration. The proliferation of an automaton (clone) was function of two factors: the degree of recognized examples (antigens), and the interactions among the automata (clones). Table 9 presents the trade-off between their immune algorithm and the biological immune system.

The fitness function, responsible for controlling the immune algorithm, took into account the fitness of the automaton at each generation, the antigen score, the automaton turnover, the network excitation and a proliferation function.

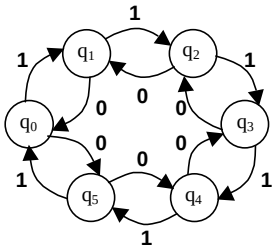


Figure 22: Deterministic finite-state automaton subject of learning.

Table 9: Mapping between the automata approach and the biological immune system.

Automata Identification	Immune System
Finite-state automata	Lymphocyte clone
Fitness of the automata	Concentration of a clone
Recognizing capacity of the automaton	Binding capability of the clone
Complementarity in the automata's behavior	Interaction between lymphocytes
Example	Antigen
Power of an example	Antigen concentration
All automata in the population	Immune network

The authors suggested that their algorithm supports more variety in the population than the standard genetic algorithm, due to a greater number of **Ag-Ab** complexes in the repertoire, i.e. more individuals with different qualities.

9.2 Genetic Programming

Nikolaev *et al.* (1999), introduced an immune version of Genetic Programming (GP). In this immune GP version (iGP), the progressive search was controlled by a dynamic fitness function, based on an analogy with a model of the *immune network dynamics*. The programs were reinforced with rewards for matched important examples and stimulated to match different examples. The fitness function consisted of two dynamic models that exerted influence on each other: a model for propagating programs that recognized more important examples, and a model for changing the importance of examples with relation to the number of programs that recognize it. The analogy between the genetic programming and the biological immune system is presented in Table 10.

The authors applied their method to a machine-learning task and a time series prediction problem. The machine-learning considered the computational induction as a problem of finding a function f from a given set of examples $\{(\mathbf{x}_1,y_1),\ldots, (\mathbf{x}_N,y_N)\}$, and the time series prediction was regarded as the inductive problem of identifying regularities among a given series of points:

Table 10: Analogy between the genetic programming and the biological immune system.

Genetic Programming	Immune System
Program	Lymphocyte clone
Fitness of the program	Concentration of a clone
Fitness proportional selection	Clonal selection process
Complementarity in the recognition potential of two programs	Interaction between two antigens
Example	Antigen
Importance of an example	Antigen concentration
All programs in the population	Immune network

…,x^t, x^{t+1},… sampled at discrete time intervals. The performance of the proposed algorithm was compared with a traditional GP system that uses multivariate trees representation models. The only difference between the two methods is that the iGP uses a dynamic fitness measure inspired in a model of the immune network dynamics.

The results presented demonstrated that the immune version attained fitter programs maintaining higher population variety (diversity) on the machine-learning and time series prediction problems tested.

10. Pattern Recognition

Pattern recognition is the research area that studies the operation and design of systems that recognize patterns in data. It encloses sub-disciplines like discriminant analysis, feature extraction, error estimation, cluster analysis, grammatical inference and parsing (sometimes called syntactical pattern recognition). Important application areas are image analysis, character recognition, speech analysis, man and machine diagnosis, person identification and industrial inspection.

10.1 A General Approach

A binary immune system model was used by Forrest & Perelson (1992) and Forrest *et al*. (1993) in order to study the pattern recognition and learning that takes place at the individual and species level in the immune system. A genetic algorithm was used to study the maintenance of diversity and generalization capability of this bit string model of the immune system, where generalization means the detection of common schemas that are shared among many antigens.

The authors used a simple binary encoding for the molecules (**Ag** and **Ab**) and the match function performed the sum of complementary bits between the strings. One interesting aspect of

this work was the use of a don't care (*) character in the definition of the antigen molecules, i.e., the strings were constructed over the alphabet {0,1,*}. This way, it was possible to study the GA's ability to detect common patterns (schemas) in the antigen population without at the same time requiring the model to differentiate between multiple incompatible antigen types.

The results presented showed that the GA could evolve an antibody type that matched multiple antigens through the identification of a common schema. In addition, by matching an antigen with multiple antibodies and then giving the fitness score to the best matched antibody, it was shown that a population could be evolved and maintained that contained representatives of different antibodies. Thus multiple peaks could be discovered and maintained in this population with this matching and scoring schemes. The mathematical results were presented in Smith *et al.* (1993).

10.2 Spectra Recognition

A general form of a chemical reaction maps a set of reactants (*R*) into a set of products (*P*). By using a binary representation, Dasgupta *et al.* (1999) described each of the reactants and products for spectra recognition. Each bit in the string corresponded to a peak occurrence within an equal length of wavenumbers.

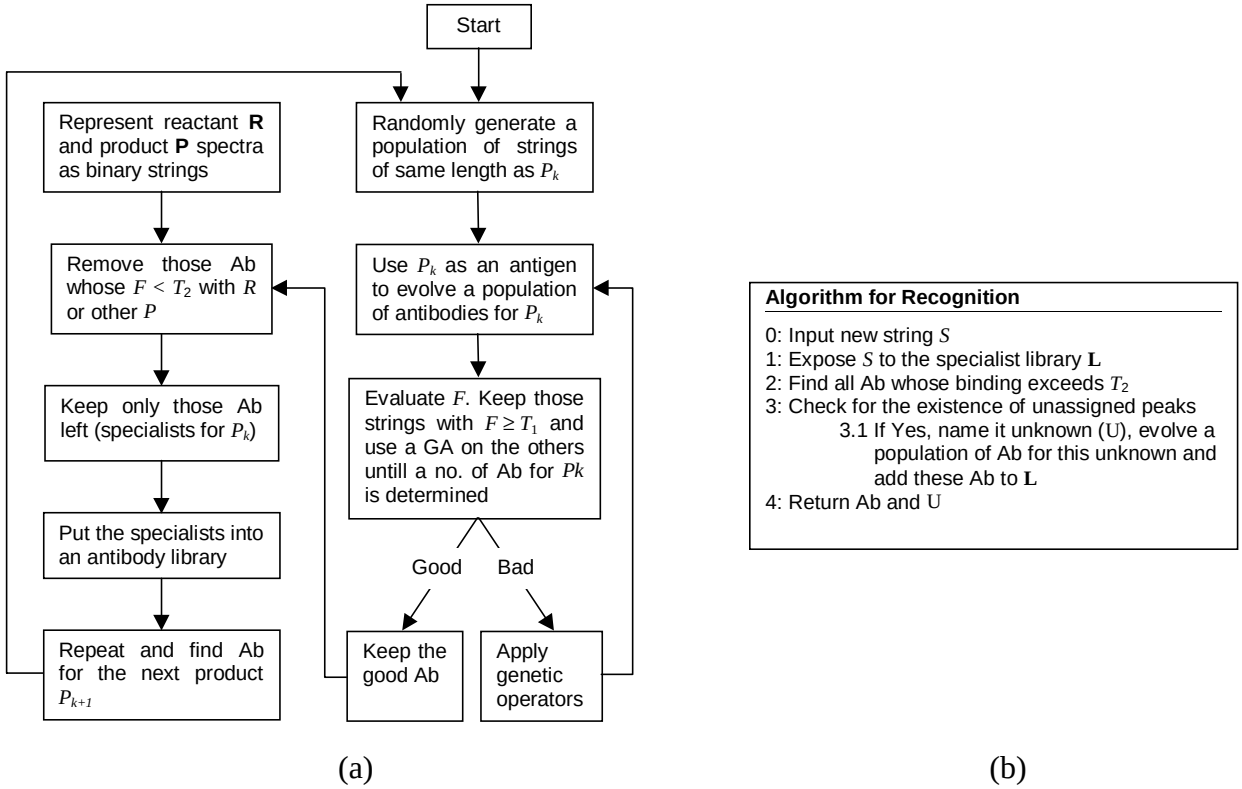
The relationship between their immunological terminology and the developed spectra recognition algorithm is described in Table 11. Equation (11) represents the match function between two bit strings.

$$F = \sum_{i=1}^{n} b_i W_i(h_i, c_i) \geq T, \qquad W_i(h_i, c_i) = h_i + c_i. \tag{11}$$

where b_i is the *i*-th bit value of the *n*-th bit in the string; T is the pre-defined threshold; $W_i(h_i,c_i)$ is the weight of the *i*-th bit as a function of the presence of a peak h_i and a characteristic property c_i.

Table 11: Immunogenetic spectra recognition.

Immune system	Spectra Recognition
Self	Set of starting reactants **R** before chemical or photochemical reactions
Non-self	Set of products due to reaction
Antigen	Any of the products **P**
Antibody	Any evolved population which uniquely recognized a single product
Matching	A match occurs if the **Ag-Ab** similarity exceeds a certain threshold *T*
Matching function	Measures how well two spectra match, according to Equation (11)



(a) (b)

Figure 23: Spectra recognition. (a) Evolving specialists. (b) Algorithm for recognition.

A typical genetic algorithm was used to create a library of specialists to perform the central administration of spectrum recognition. Figure 23(a) illustrates the proposed immunogenetic approach for evolving specialists, and Figure 23(b) describes the algorithm used for recognition.

11. Computer Models

The first models of immunological phenomena were mathematical in nature. They involved the definition of a set of differential equations that governed the behavior of the system. For good surveys on mathematical models, see Mohler *et al.* (1980) and Perelson & Weisbuch (1997). Actually, many computational-based models are being developed, among which we can detach cellular automata and agent-based approaches.

11.1 Cellular Automaton Model

A cellular automaton is a dynamic system whose evolution is completely described by local interactions, and is discrete in both space and time. Celada & Seiden (1992, 1996) and Seiden & Celada (1992) constructed a cellular automaton model of the immune system focusing on the clonotypic cell types and their interactions among each other, antigens and antibodies.

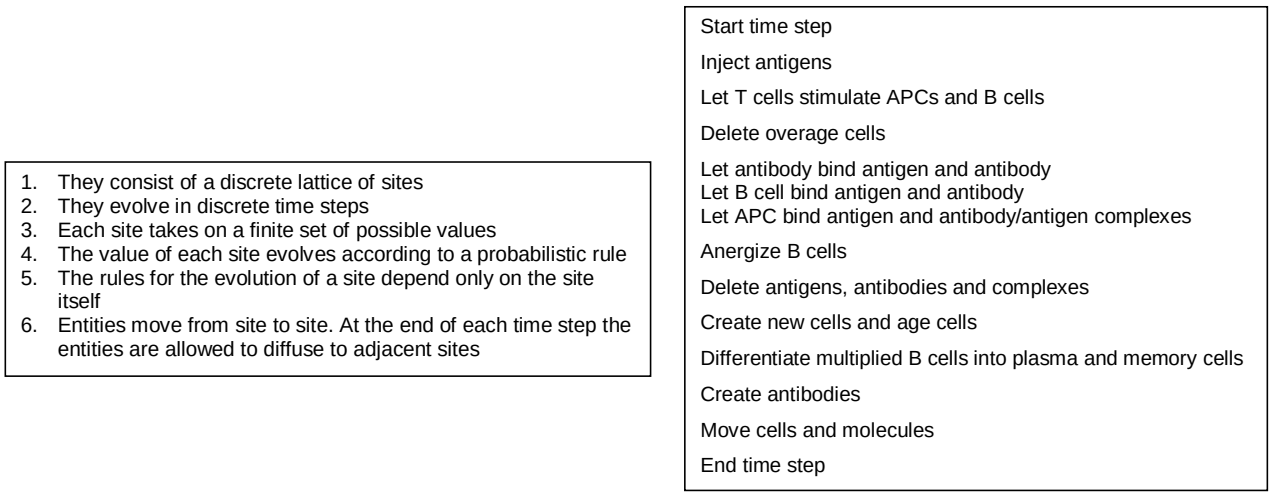


Figure 24: (a) Rules for the proposed cellular automaton model. (b) Steps in the simulation.

Their model included B and T-cells, each of which possessing a receptor represented as a binary string of *L* bits with a fixed, directional reading frame. A T-cell possessed a single *L*-bit receptor, while a B-cell had an *L*-bit receptor plus an *L*-bit MHC molecule. Non-specific antigen presenting cells were also added, with the same MHC's as the B-cells. Antigens were represented by a number of *L*-bit segments corresponding to the epitopes and peptides. Epitopes were defined as the portion of an antigen that is recognized by a B-cell receptor and peptides the portion of the antigen that can be bound by an MHC molecule and recognized by an appropriate T-cell. Antibodies were taken to have the same form as antigens, and had a paratope that was identical to the receptor of the B-cell that secreted them. There were two types of interaction between system elements. The first type was governed by specificity and the second one was non-specific, and took place between an APC cell and antigens or antigen-antibody complexes. The main rules for their cellular automaton model are depicted in Figure 24(a) and the steps in the simulation are shown in Figure 24(b). Figure 24(b) gives a more general idea of all the types of features embodied in their model.

This model was further extended to include infectious virus and cytotoxic T lymphocytes, i.e., a cellular response (Bezzi *et al.*, 1997). Bernaschi *et al.* (1998) presented a parallel implementation of the Celada-Seiden automaton discussed above.

11.2 Multi-Agent Model

Ballet *et al.* (1997) simulated a human secondary humoral response with a multi-agent system to study the kinetics of the antibody proliferation with several types of antigenic substances, like death antigens, poorly recognizable antigenic substances, proliferative antigens and antigenic substances directed against one of the immune system agents.

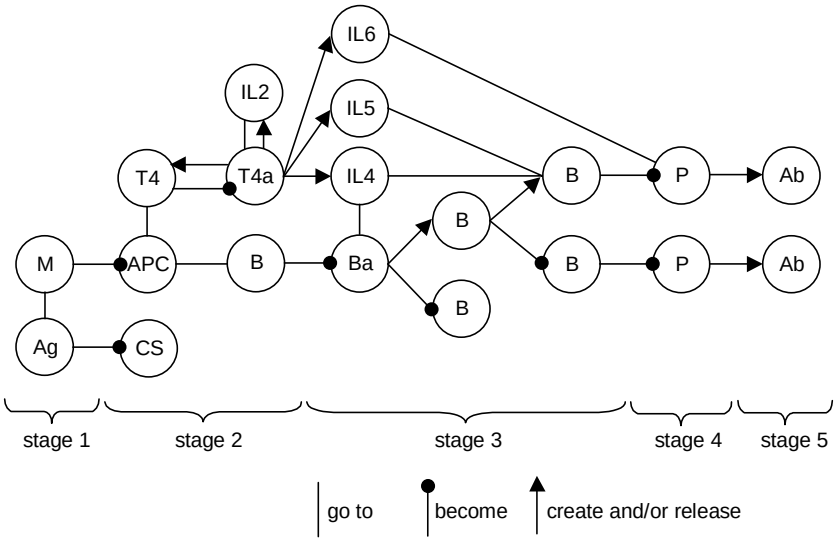


Figure 25: Multi-agent system model.

A multi-agent system was chosen because of the following reasons:

- it can describe different cells through their behavior and interaction;
- it is easy to integrate improvements and new knowledge in the model; and
- the simulations allow the study of collective phenomena without forgetting the concept of entity.

Their model embodied five different kinds of cells: macrophage (M), antigen presenting cell (APC), T CD4 cell (T4), B cell (B) and plasmocyte (P). In addition, four interleukines were used: IL2, IL4, IL5 and IL6. At last, an environment (E) that released chemotactic substances (CS) had to be defined. The relationship among the various agents composing the system is depicted in Figure 25, where index 'a' indicates an activated cell.

11.3 Disease Processes

Epstein & Axtell (1996) used a simpler agent-based model than the previous one, but their goal was studying how intra- and interagent infection dynamics could affect other social processes such as migration and trade.

In this model, every agent was born with a distinct immune system (IS), capable of adapting to a ward of diseases. The approach was based on a Hamming shape-space, where the immune systems were described by binary strings of a given length, and the diseases were of different length always shorter than the immune systems. If any substring of the immune system perfectly matched (non-complementary match) the disease, it was considered immune (or tolerant) to the disease. An immune response was simply the process whereby the immune system attempted to modify its structure locally in order to match each disease it encountered. At each time step one single bit of

the infected immune system was changed in order to reduce its Hamming distance from the infection, a process called “learning”.

An interesting aspect of this work was that the agents infected could pass the diseases to some of their neighbors, and also the diseases were able of “stealing” metabolic capacity of their hosts, a behavior like that of biological parasites. This would cause different behaviors in the “sick” agents.

Two types of rules controlled the system.

1. Agent immune response rules:

- if the disease is a substring of the IS then end, else go to the following step;
- the substring in the agent IS having the smallest Hamming distance from the disease is selected and the first different bit switched.

2. Agent disease transmission rule:

- for each neighbor, a disease that currently afflicts the agent is selected at random and given to the neighbor.

12. Other Approaches

The approaches presented in this section are all those that did not take part in the previous sections, but are considered relevant (and were available for the authors) for bringing new insights into the theory of artificial immune systems.

12.1 Open WebServer Coordination

Open WebServer is an adaptive web server and a framework for building a versatile server, which reifies various system execution policies in a web server as metaobjects. Each metaobject represents a policy for concurrency, I/O event dispatching, protocol filtering, connection management, caching, logging and service redundancy (Suzuki & Yamamoto (2000a,b)).

The works of Suzuki & Yamamoto (2000a,b) focused on the development of a Java-based framework for building an *artificial immune network*, called iNet. The iNet was used to design a policy coordination facility from the immunological point of view, where the system current conditions represented the antigens, and each quality-of-service (QoS) policy management was regarded as an antibody.

The structure of an antibody is shown in Figure 26(a), and Figure 26(b) depicts a class diagram showing the kernel of the iNet. The dynamics of the network was determined by a differential equation, based on that defined by Farmer *et al.* (1986) and further extended by Ishiguro *et al.* (1996, 1997) (see Section 2.1).

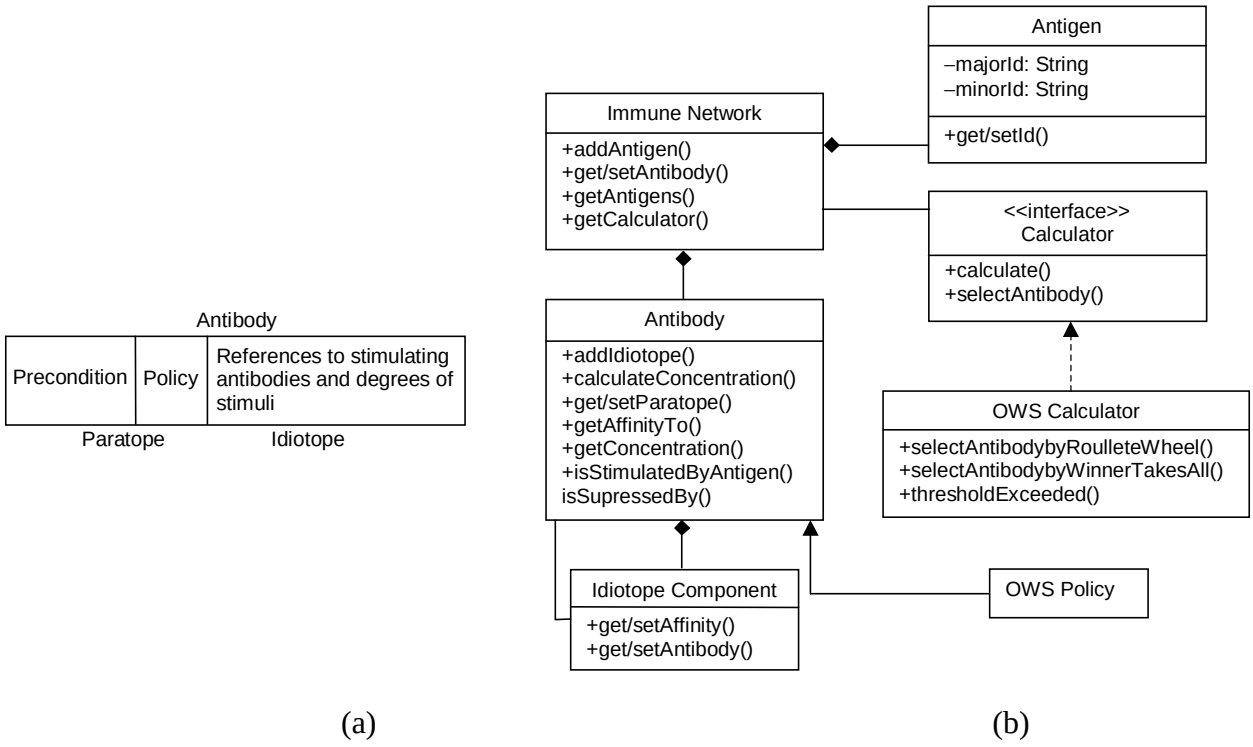


Figure 26: (a) Structure of an antibody in the iNet. (b) A UML class diagram for a kernel of iNet.

12.2 Scheduling

Hart *et al.* (1998), proposed an artificial immune system to producing robust schedules for a dynamic job-shop scheduling problem in which jobs arrive continually, and the environment is subject to changes. They investigated whether an AIS could be evolved using a GA approach, and then be used to produce sets of schedules which together cover a range of contingencies, predictable and unpredictable. Their model included *evolution through gene libraries, affinity maturation of the immune response* and the *clonal selection principle*.

An antigen represented a set of expected arrival dates for each job in the shop and hence each **Ag** described the changes that could occur and force a schedule to change. An antibody represented the schedule itself. Each antibody was produced, by randomly combining components, from an AIS which consisted of l libraries, each containing c components of s genes (see Figure 27 for an illustration). An antibody was said to match an antigen if the schedule it represented satisfied each of the fixed due dates, given the arrival dates defined in the antigen.

A GA was used to evolve an AIS, where each individual of the population represented a single AIS.

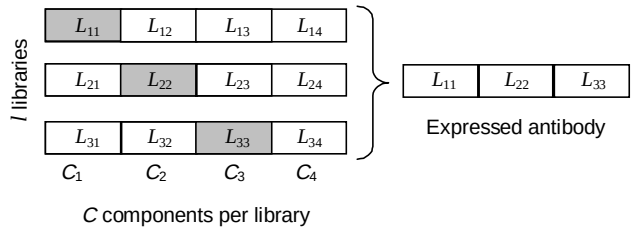


Figure 27: Generating an antibody from a set of *l* gene libraries composed of *c* components of length *s*.

The fitness of each individual (AIS) was calculated by the expression:

- express N antibodies at random and decode them into schedules;
- select K antigens at random, with replacement;
- for each k ($k = 1,...,K$) calculate its match-score and assign k the best match-score;
- average the K scores to give the overall fitness for the individual.

The authors modeled the affinity maturation of the antibody repertoire in the following way: after a match-score for an antibody had been calculated, the antibody was mutated at random in M positions, and the match-score recalculated. If the match-score improved, then the original antibody was assigned this new match-score. The clonal selection was used to create C clones of the best individual of the population, which were subjected to a hypermutation mechanism.

They concluded that the fittest schedules were obtained at low mutation rates, and high sizes of the initial population (N) and number of clones (C).

In a later work, Hart & Ross (1999) proposed a scheduling application of an artificial immune system, called PRAIS (**P**attern **R**ecognising **A**rtificial **I**mmune **S**ystem). In their system, sudden changes in the scheduling environment required the rapid production of new schedules. Their model operated in two phases. A first phase comprising the immune system analogy in conjunction with a genetic algorithm, in order to detect common patterns amongst scheduling sequences frequently used by a factory. In phase II, some of the combinatorial features of the natural immune system were modeled to use the detected patterns to produce new schedules, either from scratch or by starting from a partially completed schedule.

Their system was based on the works of Forrest *et al.* (1993) and Smith *et al.* (1993), with several additions and modifications. An antigen (**Ag**) was considered to represent a sequence of jobs on a particular machine, represented by an integer string of length L_1. An antibody (**Ab**) of length L_2 ($L_2 < L_1$) represented a short sequence of jobs that is common to more than one schedule.

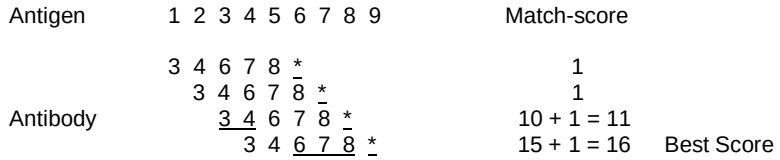


Figure 28: Integer-valued encoding for the antigen and antibody molecules, together with the matching function. A match between number corresponds to a score of 5 and a don't care corresponds to a score of 1.

The **Ab** could contain don't care alleles '*', to facilitate incomplete matching, and the fitness function constituted a modified version of the emergent fitness sharing function, in which the degree of generalization or specialization exhibited by the evolved antibodies could be controlled by altering some pre-defined parameters. The **Ag-Ab** match score took into account the presence of don't cares and the string lengths. If the string were of different lengths, the match-score was calculated for every possible alignment position, and the highest score found returned. Figure 28 illustrates the strings and their match function.

They focused on controlling the evolution of the population aiming at varying both the diversity of the antibodies produced, and the extent of the coverage of the antigen universe. They showed that the antibodies evolved could be used to reconstruct the set of original schedules that the immune system had been exposed to, and also to construct schedules that had not been seen previously.

12.3 Data Mining

Data mining, or knowledge discovery in databases, is related to the process of identifying novel, valid and potential patterns in data, where the critical issue is the extraction of knowledge from the given dataset. Hunt *et al*. (1995) and Hunt & Fellows (1996) illustrated how the immune system is inherently case-based and how it relies on its content addressable memory and a general pattern matcher to help in the identification process of new situations that are similar to past situations. They constructed a case memory inspired in the *immune system and network theory* and showed that its *pattern recognition*, *learning* and *memory acquisition* operations could support a Case-Based Reasoning (CBR) system.

Figure 29 illustrates the basic architecture of a CBR system (Aamodt & Plaza, 1994). The cases can contain any kind of information, e.g. the profile of a person, indicating its age, marital status, income, etc. In the system proposed by Hunt *et al.* (1995), an immune network represented the constructed case-base, where similar cases occupied neighboring regions in the network, and the new cases represented the antigens. Figure 30(a) illustrates the kind of encoding scheme used by the authors, and Figure 30(b) depicts their matching algorithm. Notice that the matching function took

into account the total number of matches (for each instance of a case) plus the length of the matching regions, according to Equation (12)

$$\text{Match score} = T + \sum_i 2^{l^i} \tag{12}$$

where l is the length of each region i containing more than 1 match. According to the authors, the main advantage of their method was the emergence of a network-like structure for the case-base, without the need of a detailed domain analysis to define and maintain the memory organization (case-base).

In a recent work, Timmis *et al*. (1999) applied the network-based artificial immune system described in Section 8.1 to the problem of pattern classification. Their strategy was compared to Single Linkage Clustering and the Self-Organizing Feature Maps and applied to the Iris data set of Fischer (1936).

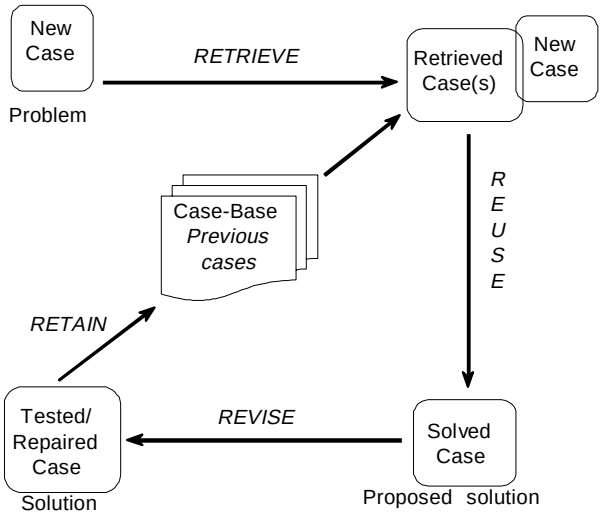


Figure 29: Case-Based Reasoning architecture.

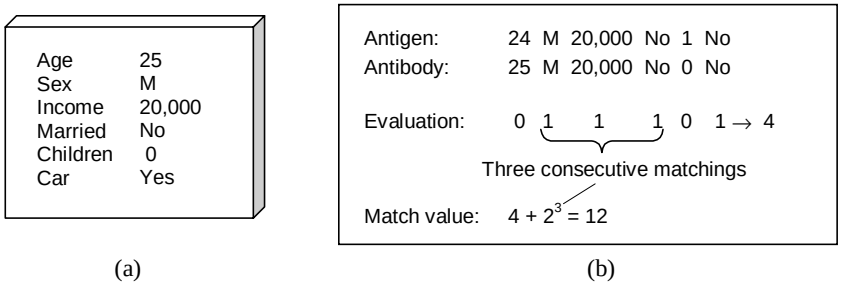


Figure 30: (a) Structure of a case (antigen or antibody). (b) The match algorithm (see Equation (12)).

12.4 Classifier Systems

Forrest & Hofmeyr (1999) pointed out a set of similarities and differences between their artificial immune system, described in Hofmeyr & Forrest (1999, 2000) and briefly discussed in Section 7.1, and the classifier systems. Although the authors suggested that the mapping between their AIS and classifier systems is not 1-1, a tentative comparison was performed according to Table 12.

Table 12: Tentative comparison between the AIS and classifier systems.

Classifier Systems	Artificial Immune Systems
Classifier condition	Detector
Classifier action	Isotypes
1,0,* matching	*r*-contiguous bits
Classifier strength	Immature, mature, activated and memory states
Message list	Network traffic (datapath triples)
Competition for packets	Bidding for messages
More specific match wins	More specific match wins
Support	Activation threshold
Message intensity	Sensitivity level
Bucket brigade	Affinity maturation
Genetic algorithm, triggering	Random detectors, negative selection

Table 13: Comparison of the major components of a classifier system and an immune system.

Classifier Systems	Artificial Immune Systems
Classifier	Antibody type
Condition	Epitope
Action	Paratope
Strength	Concentration
Specificity	Specificity
Tax	Dissipation term
Payoff	Antigen reduction
External message	Antigen
Message list	All paratopes and antigens
Economy	Concentration update rule
Performance function	Rate of antigen removal

Farmer *et al*. (1986) also pointed out a set of similarities between their immune network model and the classifier systems (see Table 13).

12.5 Sensor-Based Diagnosis

Ishida (1993) proposed an immune network model for the mutual recognition between antigen and antibody and applied it to the process diagnosis problem. In a later work, Ishida (1996a) used this same dynamical network architecture based on the idea of a chain of active state propagation found in *immune (idiotypic) networks*. The dynamical network model was elaborated as a sensor network that could diagnose sensor faults by evaluating reliability of data from sensors and process faults by evaluating reliability of constraints among data. The sensor network dynamically reacted to the on-line data from sensors. It could self-identify the unreliable sensor and constraint by moving from one equilibrium state to another, reacting to the change of the relationship among data.

The immune features he tried to use can be summarized as follows:

- recognition is performed by distributed agents which dynamically interact with each other;
- each agent reacts based solely on its own knowledge; and
- memory is realized as stable equilibrium points of the dynamical network.

A state variable r_i (and its normalization R_i) was assigned to each agent indicating its reliability. The agents composing the network were responsible for its evaluation. Figure 31 shows an example of the evaluation chain among the agents of a hypothetical network. A '+' sign indicates a positive evaluation (vote) corresponding to a reliable agent, while a '–' sign indicates a negative vote corresponding to an unreliable agent.

Considering the effect from evaluating and evaluated agents, the behavior of the network can be described by the following equation

$$\begin{aligned} \frac{dr_i(t)}{dt} &= \sum_j T_{ji} R_j + \sum_j T_{ij} R_j - \frac{1}{2} \sum_{j \in \{k:T_{ik} \neq 0\}} (T_{ji} + 1), \\ R_i(t) &= \frac{1}{1 + \exp(-r_i(t))}, \end{aligned} \tag{13}$$

where T_{ij} represents the evaluation results that can assume the values of −1, +1, −1/+1 or 0, and R_i is a sigmoid function whose exponential parameter is given by $r_i(t)$.

This equation converges to a Liapunov function like in the Hopfield (1984) network case. This way, the overall state of the system was characterized by an energy function with several local minima, making the initialization of the reliabilities a critical issue.

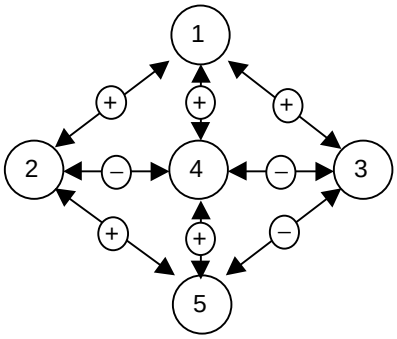
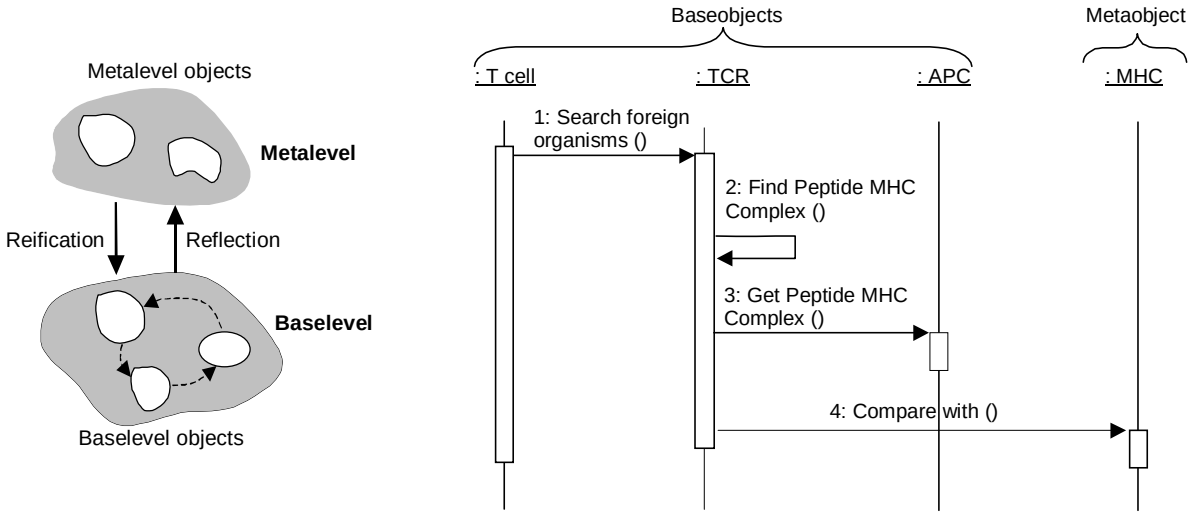


Figure 31: An example of evaluation chain for sensor-based diagnosis.

12.6 The Reflection Pattern in The Immune System

Reflection is a design principle that allows a system to have an explicit representation of itself such that it makes it easy to adapt the system to a changing environment. The base units of computation in object-oriented systems are the *objects* (or *baseobjects*). The reflection pattern generally introduces the notion of *object*/*metaobject separation*. A *metaobject* can track and control certain aspects of baseobjects. A set of metaobjects is called a *metalevel*, or *metaspace*, and a set of baseobjects is called a *baselevel*. In contrast to reflection, *reification* is the process that makes something accessible when it is normally unavailable in the baselevel. Figure 32(a) illustrates a typical reflective architecture. The reflection design can be used to draw rules of interactions among objects of any object-oriented approach, including programming languages, leading to a better comprehension and modeling of great variety of phenomena.

Suzuki & Yamamoto (1998) argued that the antigen recognition and elimination mechanism is an example of the immune reflective capability. The self/non-self discrimination problem was made equivalent to that of reflecting self in a mirror and comparing it with a foreign component. Under this perspective, MHC molecules would play the role of the mirror that T-cells could refer to in order to recognize intracellular pathogens. In the context of the reflection pattern, MHC molecules corresponded to metaobjects, while APCs and other lymphocytes were baseobjects because MHC controls the major immune phenomena including the recognition of intracellular pathogens by T-cells and activation of B-cells. Figure 32(b) presents a sequence diagram for the reflection pattern with the example of a simplified intracellular (Peptide/MHC complex) immune recognition.



(a) (b)

Figure 32: (a) Typical reflective architecture. (b) Sequence diagram for the reflection pattern in the MHC/peptide complex recognition.

12.7 Evolution of Gene Libraries

Hightower *et al.* (1995) and Perelson *et al.* (1996) used a genetic algorithm and a binary model of the immune system to study the effects of evolution on the genetic encoding for antibody molecules. One feature of their encoding was that not all genes found in the genotype (total collection of gene segments) were expressed in the phenotype (expressed antibody molecules).

The genetic material for one antibody molecule is stored in five separate component libraries. Producing one antibody molecule begins with a random selection of a genetic component from each of the libraries. In their model, the bit string representing the genotype of an individual was divided into four equal-size libraries of antibody segments as shown in Figure 33. Within each library there were eight elements, represented as bit strings of length sixteen, so each individual genome had a total of 512 bits. The expressed antibodies had a length of 64 bits.

The experiments showed that the GA could optimize complex genetic information, being able to organize the structure of the antibody libraries. They also showed that selection pressure operating on the phenotype as a whole could translate to selection pressure acting on individual genes, even though not all genes were expressed in the phenotype.

Oprea & Forrest (1998) used a similar representation as the one described above to explore how the survival probability of an individual scales with the size of its germline-encoded antibody repertoire, and extended this analysis to antibody-pathogen matching rules that might be more realistic (Oprea & Forrest, 1999).

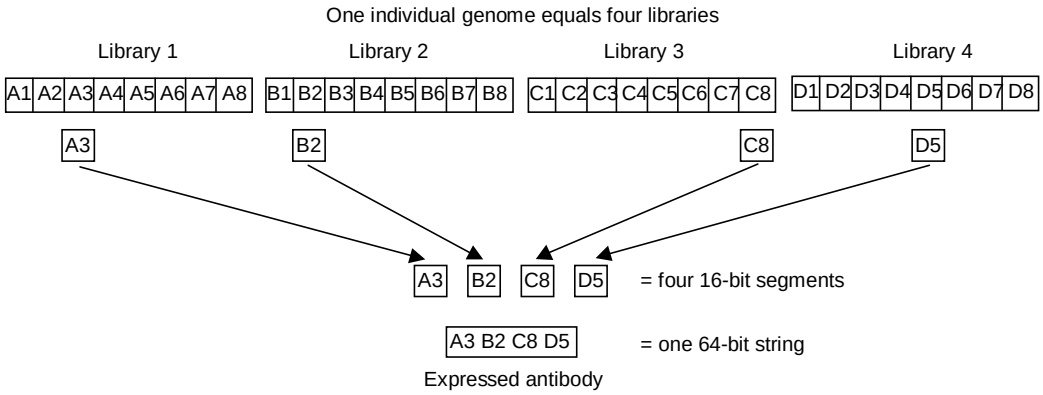


Figure 33: Process of constructing/expressing an antibody from genetic libraries.

Their results indicated that the scaling relation between fitness and the size of the evolved antibody library was only a variant of the scaling relation obtained with random libraries of same size. It was also argued that the increase in addition of antibodies to the germline-encoded repertoire did not result in a directly proportional increase in the survival probability of an individual, what could be an explanation for why the V-region libraries in various species do not seem to number more than approximately one hundred genes.

12.8 A Self-Identification Process

Ishida (1996b) presented a brief survey of applications of immunologically inspired algorithms and posed the immune system as a self-identification process.

His immunological design paradigm was stated as:

- agents should be designed so that they can be specified by the self information (program) as well as environmental conditions. Rather than incorporating all the functions needed, the program triggered by environmental conditions worked to specify the agent to fit the condition;
- a field should be designed to drive the addition or the self-reproduction of agents and to drive the specification process of each agent. It should also restrict the behavior of agents so that some of them do not disturb the harmony of the others.

12.9 A Simulated Annealing Model of Diversity

De Castro & Von Zuben (2000c) presented a simulated annealing approach aiming at generating a dedicated pool of candidate solutions that best covered the search-space. Their strategy assumed no a priori knowledge about the problem and produced a fixed-size set of potential candidates based only on the representation of the task. The algorithm induced diversity in a population by

maximizing an energy function that takes into account the Hamming distance between binary strings. Its potential to machine-learning applications and extension to Euclidean spaces were also discussed.

They considered a Hamming shape-space, where molecules were represented by binary strings of various lengths and the **Ag-Ab** interactions were measured by the Hamming distance between these molecules. The cost (energy) function proposed for the SA model allowed the detection of self-recognizing individuals and also the maximization of the Hamming distance among them:

$$D(i,j) = \begin{cases} 1, & x_i \neq x_j \\ 0, & \text{otherwise} \end{cases}, \tag{14}$$

$$F(i,j) = \frac{2}{l \times N^2} HD(i,j), \tag{15}$$

$$E = \frac{100}{2} \times \sum_{i=1}^{N} \sum_{\substack{j=1+1 \\ j \neq i}}^{N} \left(D(i,j) + F(i,j) \right). \tag{16}$$

$D(i,j)$ is a square, symmetric matrix responsible for the self/nonself discrimination, and x_i, $i = 1,...,N$, represents the members of the antibody population. It is composed of ones or zeros only, where a 0 indicates self-recognizing individuals and a 1 represents unique members (see Equation (14)). Matrix $F(i,j)$ is also a square, symmetric matrix that contains the Hamming Distance (HD) among all individuals in the population (see Equation (15)). Equation (16) is the percentile energy of the whole **Ab** repertoire, and is equal to 100% when there are no self-recognizing individuals in the population and their distance is maximal.

13. Web Sites on Artificial Immune Systems and Their Applications

In this section we are going to list some Web Sites (mostly personal Home Pages) in which to search for material on the artificial immune system and their applications. Most of these sites contain references available for download. They are ordered aplphabeticlly and a brief description of the research area of each site is given.

Derek J. Smith:
- Immune Response to Virus
- Cross-Reactivity
- Associative Memory

http://www.cs.unm.edu/~dsmith/

Dipankar Dasgupta:
- Immune System Survey
- Novelty Detection (Negative Selection)
- Book on Artificial Immune Systems and Their Applications

http://www.msci.memphis.edu/~dasgupta

Emmah Hart:
- Scheduling

http://www.dai.ed.ac.uk/daidb/people/homes/emmah/research.html

Immune System Modelling and Simulation Group
- Immune System Modelling and Simulation

http://www.cs.princeton.edu/~stevenk/
http://www.zpr.Uni-Koeln.DE/~filippo/

ISYS project:
- Formal Artificial Immune System
- Immune Network Theory
- Application to Fraud Detection

http://www.aber.ac.uk/~dcswww/ISYS/
http://www.aber.ac.uk/~jit93/
http://www.aber.ac.uk/~jot/ISYS/
http://www.aber.ac.uk/~jjh/isys/ISYS.html

Jungwon Kim:
- Negative Selection
- Intrusion Detection

http://www.cs.ucl.ac.uk/staff/J.Kim/

Junichi Suzuki:
- iNet for Open WebServer
- Reflection Pattern

URL: http://www.yy.cs.keio.ac.jp/~suzuki/project/immunity/index.html

Leandro de Castro and Fernando J. Von Zuben:
- Hybrid Approaches (neural networks and genetic algorithms)
- Learning & Optimization
- Pattern recognition and classification

http://www.dca.fee.unicamp.br/~lnunes
http://www.dca.fee.unicamp.br/~vonzuben

Mihaela Oprea:
- Immune response dynamics
- Evolution of immune receptor libraries

http://www.santafe.edu/~mihaela/

Nikolai Nikolaev:
- Inductive problem solving with immune networks

http://www.aubg.bg/faculty/cs/nikolaev/

Pascal Ballet
- Development of multi-agent systems to model immune phenomena

http://www.enib.fr/~ballet/

Patrik D'haeseleer:
- Change Detection (Negative Selection)
- Theoretical Immunology

http://www.cs.unm.edu/~patrik/

Prabhat Hajela
- Structural optimization

http://www.rpi.edu/~hajela

Stephanie Forrest:
- Immune System Modeling
- Computer Immunology

http://www.cs.unm.edu/~forrest/

Steven A. Hofmeyr:
- Computer Immunology
- Network Intrusion Detection

http://www.cs.unm.edu/~steveah/

System Sciences Laboratory (SS)
- Diagnosis
- Noise Control

http://genesis.aist-nara.ac.jp:80/work/papers/1996-e.html

Yoshitero Ishida:
- Agent-based approaches

http://genesis.aist-nara.ac.jp:80/~ishida/bcsE.html

Yuji Watanabe
- Behavior Arbitration Mechanism for Autonomous Mobile Robot

http://www.bioele.nuee.nagoya-u.ac.jp/~yuji
http://www.bioele.nuee.nagoya-u.ac.jp/~kon

14. Concluding Remarks

It can be seen from the applications presented and models discussed, that the immune system is particularly interesting for solving problems in distributed and dynamic environments. It was our main intention to provide the reader with a wide source of potential applications and inspiration for the immune-based approaches.

Like the Artificial Neural Network field, its noticeable that the Artificial Immune Systems also lead to the development of different techniques, each one mapping a different mechanism of the system. As examples we can detach the *Clonal Selection Algorithm* proposed by De Castro & Von Zuben (2000a), the *Negative Selection Algorithm* introduced by Forrest *et al.* (1994), and the *Artificial Immune Networks* as proposed by Farmer *et al.* (1986). These various mechanisms are generally used for solving different types of problems. Immune network models are suitable to deal with dynamic environments, while algorithms based upon the clonal selection principle are adequate to solve optimization problems, and the negative selection strategies are successfully applied to anomaly (or intrusion) detection tasks.

A great variety of encoding schemes and match functions was found. There seems to be no limit for the information to be inserted in the genotype (and/or phenotype) of an individual, the difficulty residing only in the problem of dealing with this information. The definition of match functions, encoding schemes and equations for controlling the dynamics of the system are problem dependent and may usually be defined in many different ways.

It can be perceived that there is no consensus within the scientific community of a unique, formal artificial immune system. As proposed in the first part of this report (De Castro & Von Zuben, 2000a), the techniques that are being named immune-based systems, negative selection algorithms, artificial immune networks, *immune engineering*, etc. all together lead to the artificial immune systems.

The references presented show that the last few years were committed by a great amount of interest and work in the AIS from many different areas of research, from medical to computer sciences. Characteristics of the immune system like uniqueness, distribution, pathogen recognition, imperfect detection, reinforcement learning and memory are very suitable for the development of systems which are dynamic, distributed, self-organized and autonomous. The areas of application are as wide as the potentialities of the system.

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