Universidade de Aveiro Departamento de Física
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Developments of the Cellular Frustration Approach to Anomaly Detection

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Engenharia Física, realizada sob a orientação científica do Doutor Fernão Rodrigues Vístulo de Abreu, Professor Auxiliar do Departamento de Física da Universidade de Aveiro e coorientação científica Doutor André Ventura da Cruz Marnoto Zúquete, Professor Auxiliar do Departamento de Electrónica, Telecomunicações e Informática da Universidade de Aveiro

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o júri

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palavras-chave

Sistemas Frustrados Celulares, Sistemas Imunologicos Artificiais, Discriminação Self/Nonself, Detecção de Perturbações Homeóstaticas

resumo

Neste trabalho é desenvolvido um método de detecção de anomalias, baseado no mecanismo da frustração celular. Este método é capaz de detectar com grande precisão desvios de um comportamento característico de um sistema complexo. Estes desvios podem ser devidos a intrusões ou a anomalias no seu funcionamento.
O método propõe ainda uma compreensão alternativa de diversos fenómenos observados em Imunologia.

keywords

Cellular Frustrated Systems, Artificial Immune Systems, Self/Nonself Discrimination, Detection of Abnormal Perturbations

abstract

This work develops a method for anomaly detection, based on the cellular frustration mechanism. It is capable of detecting accurately deviations from a characteristic behavior of a complex system. These deviations may be due to intrusions or anomalies in the system's normal functioning.
The method also proposes an alternative conceptual approach to a diverse range of phenomena observed in immunology.

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Publications

F. V. de Abreu and P. Mostardinha. Maximal frustration as an immunological principle. *Journal of the Royal Society Interface*, 6(32):321-334, 2009.

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P. Mostardinha and F. V. de Abreu. Positive and negative selection, self-nonself discrimination and the roles of costimulation and anergy. *To appear in Scientific Reports.*

Posters

Intrusion Detection in Circular Frustrated Systems: An Eminently Parallel Processing Algorithm. Mostardinha P; de Abreu Fernao Vistulo, 8^{th} International Conference on Unconventional Computation, Ponta Delgada, 2009, PORTUGAL

Modelling Homeostatic Responses. Mostardinha P; de Abreu F V, 8^{th} European Conference on Mathematical and Theoretical Biology, 2011, Krakow, POLAND

Patent

Detecção de Intrusões através de um Mecanismo de Frustracção Celular

List of Abbreviations and Symbols

APCs	Antigen Presenting Cells
CFSs	Cellular Frustrated Systems
D	Sum of the deviations from $f^{o}_{i,>\tau}$
F	Tolerance parameter
$\mathbf{f}_{i,>\tau}$	Frequency of conjugations longer than τ that is established per presenter
ILists	Interaction Lists
k	Connectivity of the agent
$\mathbf{L}_i$	Ligand of the agent i
$\mathbf{N}_D$	Number of detectors in the system
$\mathbf{N}_P$	Number of presenters in the system
$\mathbf{N}_{pops}$	Number of educated populations of detectors
$\mathbf{N}_{inv}$	Number of foreign ligands tested
P	Probability of a detector of an arbitrary population avoiding a ligand displayed by a presenter having high affinity for it
$\mathbf{p(L}_i\mathbf{, j)}$	Position of the ligand L_i in the agent j IList
$\mathbf{P}_{>\tau}$	Probability that each presenter establishes a conjugation longer than τ iterations
$\mathbf{p}_{ndet}$	Probability of detection evasion
$\mathbf{n}_{\mathcal{R}\geq 1}$	Number of presenters with $\mathcal{R} \geq 1$
$\overline{n_{\mathcal{R}\geq 1}}$	Average number of presenters with $\mathcal{R} \geq 1$
Pert	Perturbation imposed

$\mathcal{R}_i$	Detection ratio
$\mathbf{R}_i$	Receptor of the agent i
$\mathbf{S}$	System simulated
$\mathbf{s}_{A_i}$	Interaction state of the agent i
τ_{an}	Anergy time
τ_1	$0.15 \times \tau_{ed}$
τ_2	$0.30 \times \tau_{ed}$
τ_3	$0.60 \times \tau_{ed}$
τ_{sep}	$1.5 \times \tau_{ed}$
TCR	T Cell Receptor
τ_{ed}	Threshold time corresponding to the education process
τ_{neg}, τ_{pos}	Threshold time corresponding to the negative education process and the positive education process, respectively
τ_{an}	Anergy time
$\mathbf{W}_{DET}$	Detection window
$\mathbf{W}_{ED}$	Education window

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1 Introduction and Motivation

The purpose of this thesis is to develop a method that detects deviations from normal behavior of a complex system. The need for a method that may be applied in different contexts, trustable and easy to implement makes the challenge complex but, at the same time, extremely relevant. Computer security, chemistry and medicine are a few examples of fields in which complex strategies are needed to detect deviations from a system's normal behavior.

To better understand the complexity of this task, an analogy with proofreading a text can be enlightening. Proofreading a text is also an anomaly detection task. In what respects orthography, a check of every word against the contents in a dictionary seems to solve the problem. Although the number of entries is huge, different strategies can be thought to facilitate finding each word in the database, a task that can be quickly accomplished. In this sense, the text could be verified word by word, and mistakes due to misspellings or use of words that do not exist are easily detected. However, other issues need to be considered in the task of verifying a text.

The correction of a text comprises other issues, namely grammar considerations, concordance of gender, number, etc., and even a more difficult one, the analysis of the meaning of each word in the sentence in that specific context. In the case of concordances, all the possible combinations of words allowed or alternatively all the combinations of words forbidden could be listed, together with the words of the language - considering that the storage of all this information is possible. Concerning the analysis of meaning, the structure of the sentence can be correct, all words can be spelled correctly, however their association in a given context can be incorrect. In this case, databases can not detect this type of anomalies.

This simple example clearly illustrates problems that anomaly detection systems

face when monitoring complex systems. In complex systems the number of patterns required to code the normal behavior is huge. Just alike, the number of potential anomalies is also enormous. In addition, it is also expected that this approach should integrate all the features of an anomaly detection system: it should respond against unseen patterns or wrong association of patterns.

The previous example of the text can be easily translated into a new scenario, in which the words in a text are displayed by cells in interaction; the idiom that rules the legitimate behavior is encoded in the interactions among cells, and the system that detects anomalies in the text works as an immune system. A quick search on the web about what the immune system is returns the following generic definition: "A system of biological structures and processes within an organism that protects against disease"*. In order to function properly, an immune system must detect a wide variety of pathogenic derived antigens, arising from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue.

It is widely accepted that the immune system works to keep the body healthy. What is not consensual is how this is accomplished. Is this done by reacting against what does not belong to the body and, if this is the case, how perfectly can this be achieved? This is the basis of the so called self/nonself discrimination dilemma. There are textbooks that maintain that this discrimination is imperfect [1], while others argue that a better explanation is required [2]. The discrimination self/nonself is "excellent but imperfect" ([1], p. 71), or "immunology is still struggling to explain major phenomena such as discrimination of self from nonself" ([2], p. 726). In any case it would be important to know if there is any mechanism that could guarantee that perfect self/nonself discrimination could be achieved under immunological plausible conditions. This could have important implications as it could have worked as an important evolutionary force that shaped the development of the immune system.

The immune system has served as inspiration to explore different approaches in the research of anomaly detection systems. However, up until now, none of the approaches performs perfect discrimination self/nonself for systems with arbitrary diversity [3–7]. To some extent, it has been questionable the relevance of these approaches for computer security [8].

In the computer security field several other approaches have been proposed for anomaly detection. Some use bayesian statistical analyses; others use databases for

*http://en.wikipedia.org/

the detection of foreign elements [9–11]. The first approach has the major advantage of detecting illegitimate behaviors similar to legitimate behaviors. However, it has difficulties to decide if deviations from "normal" behavior are fluctuations or anomalies. The system only reacts when the anomalies have a significative impact on a few features of the system's behavior. Typically, these approaches lead to large numbers of incorrectly signaled events (false positives), while the number of not signaled anomalies (false negatives) is also low.

The approach based on the detection of foreign elements can be divided into different perspectives: detection of anomalies already known and detection of unknown anomalies. The methods based on detection of anomalies already known require that all anomalies are stored in a database so that they can be recognized. The storage of all the possibilities is impossible, because the number of anomalies is huge and new anomalies are always appearing. Thus, the database should be continuously updated so that the most relevant anomalies remain, while others are discarded. In addition to this limitation, they can not detect new anomalies in the system. Anomalies that were not in the database are classified as legitimate, so there is always a considerable number of mistakes in the approach.

In this thesis, we propose a new method of detection that is closer to the last class of methods. The singularity of this method is that it detects simultaneously different types of anomalies that the remaining methods do not detect. To do so, it takes advantage of a new organizing principle for complex systems to generate a dynamical system of agents in interaction. The deviation from the "normal" behavior of the system emerges from the complex dynamics of the population of agents in interaction. An anomaly is promptly signaled by a type of generalized proofreading mechanism embodied in the method [12–16]. This approach ensures perfect detection against invaders with total tolerance towards self agents. This kind of detection can be combined with the detection of abnormal configurations of legitimate agents. These features make the approach relevant for applications in anomaly detection in different areas, but also increase the understanding of potential mechanisms ruling the adaptive immune system in a physicists' sense. Due to the fact that this approach is based on an agent-based dynamics, no information concerning anomalies needs to be stored and the number of mistakes due to false positive or false negatives is minimized. The detailed discussion of this approach is the goal of this work.

This thesis is divided into chapters according to the topics discussed. In the next chapter basic immunology concepts that inspired the model will be briefly

presented, followed by the introduction of the Principle of Maximal Frustration which rules the dynamics responsible for the detection mechanism. Afterwards, the model is presented by a set of definitions which clearly point out the most important details. After this, the agent-based model and the associated algorithm is presented. This is crucial for understanding the model developed. The Background Theory chapter ends with the discussion of the main concepts related to the model, which is discussed and compared in some respects with other models and other conventional immunological perspectives. In the following chapter, the validity of the results obtained by the cellular automata approach are discussed and compared with the results of the mean field equations. The Main Results chapter presents an exhaustive collection of results concerning different issues. The chapter starts with the first system developed in this thesis and the main results concerning intrusion detection are presented. After this, the results are presented in several sections covering detectors repertoire education (positive and negative selection process) and later anomaly detection. This work ends with a final discussion in which the main achievements are presented, and the perspectives for future work proposed.

2 Background Theory

2.1 Basic Immunology Behind Cellular Frustrated Systems

The immune system is, as mentioned before, the inspiration for the modeling of an intrusion detection system based on the cellular frustrated ideas. For this reason, it is necessary to understand which are the essential mechanisms that the immune system uses to achieve its purpose. In this chapter only a brief description of the main issues that will be integrated in the system will be presented, not an exhaustive exposition of all the details of what is known in immunology. Throughout the thesis the topics discussed here will be revisited and their meaning will be discussed in the frustration framework.

In mammals, the immune system is a complex system in which proteins, cell and organs interact in a complex network of interactions with the aim of protecting the body from a wide range of potential threats such as microbes, viruses, etc [1, 17]. The immune system provides two main mechanisms of defense which interact cooperatively: the innate immune system (also called natural or native immunity) and the adaptive immune system (specific or acquired immunity). The innate immune system provides the first defense against invaders. If invaders are not blocked by anatomic barriers, innate immunity provides a response where specialized cells are activated ingesting these invaders. These responses are non-specific and eliminate a big number of invaders. When the innate immune system fails for some reason, the adaptive immune system receives a stimulus from the innate immune system and it begins its action. In opposition to the innate immune system, the adaptive immune system is adaptive, acquired and specific. This means that it can evolve during the

lifetime, constantly adding patterns to its repertoire of defense, as well as increasing the specificity of the recognition of a given foreign pattern [1, 17].

Adaptive immune responses are provided by cells named lymphocytes, which are activated when they recognize antigens. Lymphocytes develop from stem cells but they have two different lineages: in bone marrow and another in thymus, which generate mature B lymphocytes and mature T lymphocytes, respectively. B lymphocytes recognize soluble or cell surface antigens and differentiate into antibody-secreting cells [1, 17]. However, this thesis is not concerned with this type of response, it will focus on the initiation of the immune system response by T lymphocytes.

T lymphocytes, as referred to earlier, mature in thymus[1, 17]. Mature T lymphocytes recognize in their receptor only antigens presented in specialized molecules called major histocompatibility complex (MHC) molecules, which exist on the surface of Antigen Presenting Cells (APCs). Antigen Presenting Cells are specialized cells that capture microbial antigens in the body and transport them to peripheral lymphoid tissues where these cells present the antigens to the T lymphocytes. APCs are also responsible for the activation of T Lymphcytes. This specific antigen recognition in T lymphocytes is performed by a cell surface protein called T cell receptor (TCR). T Cell receptor could be able to bind and to recognize antigens in a close range of affinities. The recognition of all the potential antigens demands that the TCR should be prepared to cover an enormous diversity [1, 17].

The receptors diversity of T lymphocytes is generated in the maturation process, which all T lymphocytes undergo. This maturation process comprises three main stages: proliferation of immature cells, expression of antigen cell receptors and of lymphocytes that express useful antigen receptors[1, 17, 18]. Firstly, in the maturation process there is a huge proliferation of immature T lymphocytes. This increase in number favors the expression of valid antigen receptors for a larger number of cells. This process will occur in other moments of the maturation process. Secondly, the expression of the antigen receptor occurs. The antigen receptor has variable regions that are originated by somatic recombination of the gene segments. This process is responsible for the diversity of the antigen receptor of the immature T lymphocytes. These two stages alternate in cycles in which functional antigen receptors are selected and proliferated, and those lymphocytes that fail the expression of the antigen receptor die, because they do not receive the necessary survival signals. Finally, in the last step of the maturation process, T lymphocytes undergo

a final test to check the recombination of receptors: the positive and negative selection. If thymocytes are enable of interacting with self-peptide-MHC complexes, they undergo programmed cell death, a mechanism known as death by neglect [19]. In these way only a fraction of thymocytes are positively selected and proceed to the next stage of the development process. During negative selection, the same fate happens to lymphocytes that strongly bind with antigens, lymphocytes die by apoptosis. T lymphocytes with high affinity can start responses against cells of the body and for this reason they should also be eliminated. From this maturation process, a repertoire of T lymphocytes emerges with huge diversity of antigen receptors, which ensures a prompt attack against invaders and moderate affinity against self antigens and, consequently, total respect for what belongs to the body [1, 17].

After the maturation process, T lymphocytes are prepared to leave the thymus and to start their task of searching for antigens in the periphery and starting an immune response if necessary. The immune responses have sequential phases, which are: the recognition phase, the activation phase, the effector phase, the decline and memory [1, 17]. This work will focus on the recognition and activation phase of the immune response. Further work is needed to cover the other phases of the immune response.

The recognition phase takes place in lymph nodes [1, 17]. There mature T lymphocytes can locate and recognize antigens using their antigen receptors. However, this recognition is not enough to trigger the first phase of the immune response. At least a second signal is required in order to activate the lymphocyte. According with the current view, the second signal is provided by microbial products or by products generated by the innate immune responses to them. It is called costimulator because it acts as a stimulator in the presence of the antigen. If the second signal is absent, the activation fails and the T lymphocyte becomes unresponsive. This can also happen if the second signal that was provided is not the appropriate one. The unresponsive state is designated as anergy. The anergy state is thought of as a tolerance mechanism that avoid responses against self antigens[1, 17].

All the processes presented above are the basis of a remarkable discrimination task performed by the adaptive immune system. On the first hand, the immune system can be triggered against an invader, the source of nonself peptides and simultaneously maintain total tolerance against all the cells of the body sources of self peptides. The task of discriminating self and nonself antigens is a hard one because no a priori essential differences exist between them and yet the required response

needs to be specific. This recognition of the immune system is called self/nonself discrimination [1, 2, 17].

In spite of the large accumulated knowledge of the many mechanisms ruling the immune system, an integrative view of the main processes involved is still needed. Even today questions about basic issues lack coherent answers. Some of them we addressed in this work. For example: Why are positive or negative selection required? What is the role of anergy and costimulation for the activation of the immune response? What is the importance of the generation of diversity of T cell receptors for the protection of the host? The model that will be studied in this thesis will give new insights to these questions with the benefit of proposing an integrative view of the Adaptive Immune System.

2.2 Maximally Frustrated Systems and the Principle of Maximal Frustration

CFSs are a group of complex systems in which elements interact according to the Principle of Maximal Frustration [15, 20]. In Cellular Frustration Systems only two main assumptions are made: a) Cellular responses should be modeled as cellular decisions; b) Cellular responses require a finite amount of time to take place. Any element of the system interacts and potentially reacts with all the other elements. However, instead of instantaneous memoryless reactions, each cell performs decisions during which it interacts with other cells and each cell can change pair to optimize its previous conjugations. A reaction will only take place if two elements form a stable interaction that lasts longer than a threshold time.

These two assumptions are not only theoretical concepts, they have also gained experimental support. It is already reported that the polarization of an APC can be changed according to different stimulus provided by the cells with which it is interacting. Experimental work shows that when a T cell is interacting with an APC and another APC appears, the T cell stops the interaction with the first APC and starts a new interaction with the second APC. Both APCs are equal, but the second one has more peptides expressed [21, 22]. This could be seen as a probabilistic fact. The T cell could have a given probability of remaining or changing conjugation [23]. Alternatively, this change can be seen as a decision process, according to which the T cell is always trying to interact with the cells providing the stronger stimulus.

This is the view put forward by the CF framework.

Concerning the assumption that establishes that the time of the interaction is crucial to trigger a response, recent experiments [24–27] indicate that the duration of the antigen receptor signaling is crucial for T Cell activation or tolerance. Brief T Cell-APC interactions result in tolerance, while prolonged interactions are associated with activations and the development of effector cells.

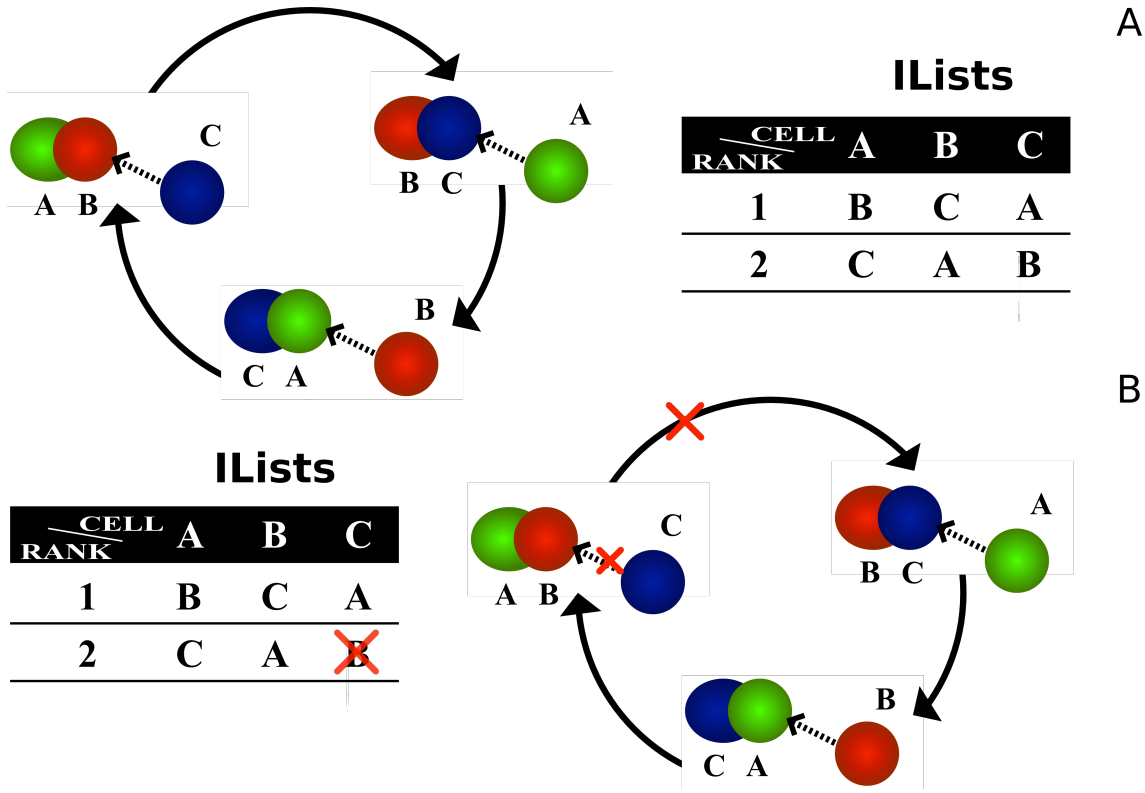


Figure 2.1: Decision dynamics for three agents: (A)ILists and the frustrated dynamics; (B) if cell C does not interact with cell B, then cross-reactivity is reduced but the system's reactivity increases.

The assumptions made in the CF framework lead to new ideas concerning reactivity, tolerance and activation; there are emergent concepts resulting from the dynamics of cellular frustrated systems. In order to better understand these concepts in the CF framework, a simple frustrated system is represented (Figure 2.1A). For simplicity, only three cells interacting and establishing conjugations are considered. All cells are very reactive and they always try to form stable conjugations with a cell at a time. Conjugations between cells are decided according to an interaction list (IList) for each cell, which ranks all the other cells in order of decreasing affinity. In maximally frustrated systems the IList of each cell is built in such a way that

on the top of its IList each cell has the cell that has it at the bottom of the IList - while cell A has cell B on the top of its IList, cell B has cell A on the bottom. This structure generates a maximal frustrated dynamics. If cell A and B are conjugated and cell C is alone, cell C can destabilize cell B, the conjugation AB being destroyed. While agent A is very satisfied because it is conjugated with the agent that is placed in the top position of its IList, agent B is very dissatisfied due to the fact that it is conjugated with the agent that occupies the bottom position of its IList, and consequently, if given the chance, changes conjugation. A new conjugation BC is formed and cell A turns into a non-conjugated state. Cell A is said to be frustrated with the presence of cell C, because it could have a long-lived conjugation in the absence of cell C. Each cell that is in a non-conjugated state tends to destabilize the conjugation, so cell A destabilizes cell C that is in conjugation BC. Because of the fact that cell A is ranked in the first position of cell C IList, cell C decides to finish the conjugation with cell B and starts a new conjugation with cell A that is alone and accepts any cell to pair up with. This frustrated dynamics goes on and on. Cellular frustrated systems never reach stable states, they live in steady states in which conjugations have characteristic lifetimes. If a response needs a time longer than this lifetime to be triggered, no reaction will take place. Although all cells are very reactive and are always trying to establish conjugations, an unresponsive state is built using reactive cells.

Another interesting outcome of this framework is the effect of the reduction of the reactivity of one cell on tolerance - for example by blocking one interaction. If the interaction between C and B is forbidden, the conjugation AB becomes stable and this lifetime increases, because no other cell can destabilize this pair (Figure 2.1B). This increase in lifetime is enough to trigger a response.

In CFSs if the reactivity of one cell is reduced, the tolerance of the system decreases and the system can change from a tolerant state to a reactive one. This decrease of tolerance is the result of a decrease in the frustration of the system. In maximally frustrated systems, conjugation lifetimes are minimum and conjugation rates are maximal. When a cell decreases its frustration, its characteristic lifetime with another cell increases and the dynamics signals this change. Hence, reactivity and tolerance are emergent properties of CFSs. Despite the fact that all the cells of the systems remain the same, a tolerant or a reactive state can emerge according to the composition and dynamics that is generated in the system.

The decrease of frustration in the system is also the response of CFSs relative

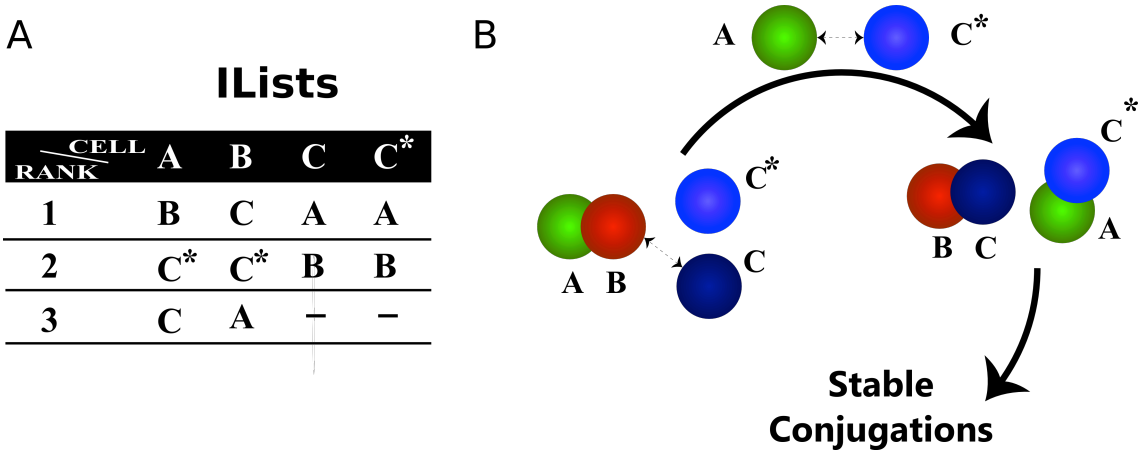


Figure 2.2: Intrusion in CFSs: (A) ILists of the system and (B) comparative destabilizations in conjugations involving the invader.

an invader. An invader can be a cell that is a copy of another cell of the system and that interacts according to an IList that is also copied from, a given cell, for instance the first cell. Considering the invader as - C* - a copy of cell C, C* behaves as C. However, C* was never been seen in the system and consequently cells A and B place it in a random position in their ILists. Let us consider that both cells put C* in the middle position of the ILists (Figure 2.2A). Only this small change in ILists is enough to have a dramatic effect on the dynamics of the system (Figure 2.2B). The introduction of C* leads the system to a stable state in which the cells in conjugations BC and AC* do not optimize anymore. This final configuration is independent of the initial conjugate considered. This stability in dynamics is easily confirmed through a very simple mathematical analysis.

Considering the above system with the three cells, A, B, C, typical lifetimes should be determined. The normalized frequencies of conjugated or single cells, are given by n_{ij}=N_i/N, in which N_{ij} is equal to the number of conjugations between i and j or the number of alone i cells, when j=ϕ. Here N is the total number of cells in the system. Dynamical equations valid in the mean field sense can then be written when i=A and j=B, as:

$$\frac{dn_{AB}}{dt} = n_{A\phi}n_{B\phi} + n_{B\phi}n_{AC} - n_{AB}n_{C\phi} \tag{2.1}$$

in which the positive terms consider the creation processes and the negative ones their destruction. The remaining equations are obtained by substitutions (A, B, C)→(B, C, A). These equations are valid a part from a time scaling factor. For the

purpose of computational applications one scale time according to time, iterations. Then, from one time step to the next, the normalized frequencies change according to:

$$n_{ij}(t+1;t_0) \simeq n_{ij}(t;t_0) + n_{ij}(t;t_0) \times \tau_{F_{ij}}^{-1} - n_{ij}(t;t_0) \times \tau_{D_{ij}}^{-1} \tag{2.2}$$

in which $\tau_{F_{ij}}^{-1}$ is the rate of formation of conjugates and $\tau_{D_{ij}}^{-1}$ is the rate of destruction of conjugates that dictate the lifetime of each conjugation. In the case of AB conjugation it can be written:

$$\tau_{D_{AB}}^{-1} \sim n_{C\phi} \tag{2.3}$$

When the invader is introduced in the system - C*-, the equations change with the addition of the term relative to the invader. Thus:

$$\tau_{D_{AB}}^{-1} \sim n_{C\phi} + n_{C^*\phi} \tag{2.4}$$

$$\tau_{D_{BC}}^{-1} \sim n_{A\phi} \tag{2.5}$$

$$\tau_{D_{AC}}^{-1} \sim n_{B\phi} + n_{C^*\phi} \tag{2.6}$$

$$\tau_{D_{AC^*}}^{-1} \sim n_{B\phi} \tag{2.7}$$

The symmetry of the system is broken due to the introduction of the invader in the middle position of ILists. The destabilization of conjugations is only performed by the non-conjugated cell, as shown by the rates of destruction of each conjugation. Nevertheless, the introduction of the invader leads the system to a stable state in which all cells are conjugated: AC* and BC. Cells B and C* are conjugated with their top preferences, so they do not want to change conjugation. Due to this fact, cell A accepts C* that is its second choice and cell C is forced to be with B because cell A prefers to be with cell C*. Thus, normalized frequencies of non-conjugated species are zero, and the conjugation lifetimes - which are in inverse proportion to the rate of conjugates destruction - are infinite, due to the fact that there are no cells that destabilize both conjugations.

The toy model here presented suggests that Cellular Frustrated Systems could be a promising framework to model intrusion detection systems. The development of CFSs as intrusion detection systems is the aim of this work.

2.3 Theoretical Model

The model here developed considers that a complex system has a normal behavior which can be coded into a computational system of agents in interaction - Cellular Frustrated System CFS (Figure 2.3).

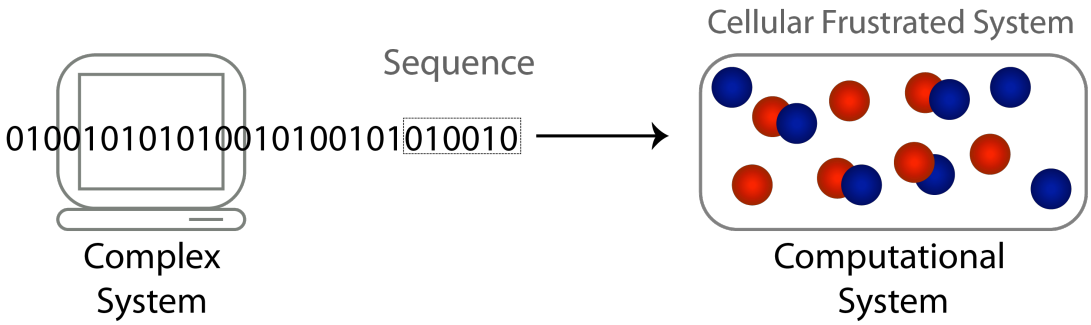


Figure 2.3: Binary information extracted from a complex system can be coded into sequences. These sequences that characterize the normal behavior of the complex system is used in the computational system of agents in interaction (Cellular Frustrated System). Every change in the complex system changes the dynamics of the agents in interaction. This change in the dynamics of the computational system triggers events that signal a corresponding change in the normal behavior of the complex system.

In CFSs only two main assumptions (section 2.2) are required to build a computational system of agents in interaction, in which every change in the complex system changes the dynamics of the agents in interaction. This change in the dynamics of the computational system is the triggering event that signals a corresponding change in the behavior of the complex system, that can be due to different causes.

CFSs use the immunological inspiration of some mechanisms of the adaptive immune system in a minimal model that considers APC and T cells defined in the computational system as presenters and detectors, respectively. The inspiration is extended to the function of these agents in the model [1, 17, 28]. Presenters display information extracted from the complex system to detectors. Detectors recognize this information and are triggered or not, leading to a response according to the information presented.

The computational model here developed considers only two different types of agents, instead of the three types considered in the previous section (Figure 2.4). The frustration in this system with 2 types is ensured because there are differences in all agents within a type. These differences allow each agent to optimize among

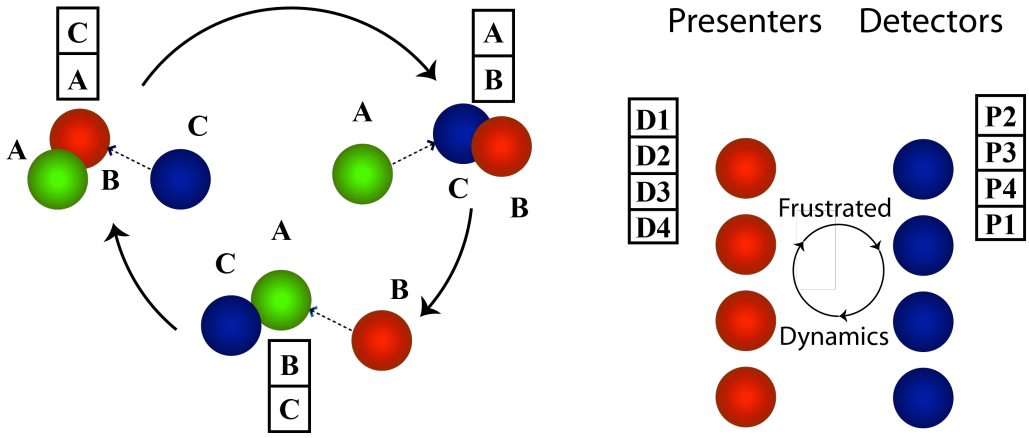


Figure 2.4: Left: Decision dynamics, ILists and the frustrated dynamics for a model with three types of agents, . Right) System with 2 types of agents. The frustration in this system with 2 types is ensured because there are differences in all agents within a type, which force agents to change conjugation due to interactions with agents of the opposite type.

the agents of the opposite type. The interaction rule of Cellular Frustrated Systems is maintained, each agent always tries to establish a conjugation with a preferred agent. With the same interaction rules and due to the differences among agents, a frustrated dynamics is also generated in systems with 2 types of agents.

To make the understanding of the model easier, the presentation of the main concepts of CFSs will be initiated with a section of generic definitions. After this, the algorithm implementation will be carefully described. Finally, the fundamental ideas that differentiate this framework will be discussed.

2.3.1 Model Definitions

The computational model is based on a frustrated dynamics of agents in interaction. Due to the immunological inspiration of the computational model, the agents' set (A) is divided into two different sets according to the agents' type: presenters (P) and detectors (D), such that: A = P ∪ D and P ∩ D=∅. Each type of agents has a fixed and equal number of elements, such that N_A=N_P+N_D and N_P=N_D.

Definition 1. ***Agents*** *An agent, A_i, is a basic element of the dynamics of interactions defined by $\forall A_i \in A$, A_i=$\{T_i, L_i, R_i, k_i, C_i\}$, in which:*

- *T_i is the type of agent, $T_i \in \{Presenters, Detectors\}$;*

- *L_i is the ligand of the agent, $L_i \in \{1, 2, \ldots, L_{MAX}\}$, with L_{MAX} defined as the maximal value in the presenters or detectors space of ligands;*
- *R_i is the receptor, which can be coded by an Interaction List(IList) that is the ordered set of all the ligands of the opposite agent type in decreasing order of affinity ;*
- *k_i is the connectivity, which corresponds to the number of different ligands from the opposite agent type with which the agent interacts, $k \in \{1, \ldots, N_{A/2}\}$;*
- *C_i is the connectivity list in which all agents with which the agent interacts are listed.*

Due to the fact that detectors should be continuously checking the information presented by presenters, it is crucial to promote interactions between presenters and detectors. Thus, presenters interact only with detectors and detectors interact only with presenters. Interactions between agents from the same type are not allowed. In addition, each agent interacts only with an agent at a time.

All agents interact according with the same interaction rules. In order to simplify the presentation of the interaction rules, the interaction state and the ranking in the other agents' IList will be associated to each agent :

- s: the interaction state; indicates if an agent, A_i, is in an interaction and with which agent, such that $s_{A_i} \in \{0, 1, \ldots, N_A\}$. If it is conjugated with A_j, $s_{A_i} = A_j$, if A_i is alone, $s_{A_i} = 0$.
- p: the position in the IList; indicates the position of ligand L_j in the agent i IList, such that $p(L_j, i) \in \{1, 2, \ldots, \#(IList_i)\}$. If L_j is in the top position of the IList of A_i, $p(L_j, i) = 1$. On the contrary, $p(L_j, i) = \#(IList_i)$ if L_j is placed in the bottom position of the IList of agent A_i .

The interaction rules which generate the dynamics of decisions among agents are defined as:

Definition 2. ***Interaction Rules*** *Considering two agents from opposite types, a_i and a_j, they will start a new interaction if:*

- *if* $s_{A_i}=0 \wedge s_{A_j}=0$
- *if* $s_{A_i}=0 \wedge s_{A_j}\neq 0 \wedge p(L_{A_i}, j)>p(L_{s_{A_j}}, j)$
- *if* $s_{A_i}\neq 0 \wedge s_{A_j}\neq 0 \wedge p(L_{A_i}, j)>p(L_{s_{A_j}}, j) \wedge p(L_{A_j}, i)>p(L_{s_{A_i}}, i)$

All agents are always trying to establish interactions with the agents in the top positions of the IList. If an agent is alone, it will accept any agent of the opposite type. Nevertheless, if it is interacting, it will change pair only if a preferred agent appears. The interaction lifetimes between agents have a crucial role in the triggering of the activations in this model. It can be defined as follows:

Definition 3. ***Interaction or Conjugation Lifetime*** *The interaction or conjugation lifetime of an interaction is the number of iterations between the formation and the destruction of a given interaction between 2 agents of opposite types.*

In the same way that it is possible to define the Interaction Lifetime, the inactivity lifetime can also be defined:

Definition 4. ***Inactivity Lifetime or No-Conjugation Lifetime*** *The inactivity lifetime corresponds to the number of iterations that an agent remains without establishing any interaction with an agent of the opposite type.*

In CFSs interactions between agents should have minimal lifetimes and the interactivity among agents should be maximal, with minimal inactivity lifetimes, so that small perturbations in dynamics are noticed. In order to maximize the frustration in the dynamics, detectors should undergo an education process. This process selects a repertoire of detectors which is capable of interacting with presenters in interactions with minimal lifetimes. Two different processes of selection are considered. One in which agents that do not interact are eliminated and replaced by others in a process called positive education. The designation of the process is inspired by the education process that is operated in the real immune system. It is defined in the computational model as:

Definition 5. ***Positive Education*** *Every detector (D_i) that does not establish interactions longer than a threshold time - τ_{pos}, $\tau_{pos}\in\mathbb{N}$- is eliminated and replaced by another arbitrary detector (D'_i) such that $T_{D_i}=T_{D'_i}\wedge k_{D_i}=k_{D'_i}$, $L_{D'_i}$ and $R_{D'_i}$ are randomly drawn and $C_{D'_i}$ is changed accordingly.*

The second process operates in detectors that establish interactions with the longest lifetimes, which are replaced by new arbitrary detectors. This process is called negative selection, because it is inspired in the negative selection process that is operated in the immune system. In the computational system it can be defined as:

Definition 6. ***Negative Education*** *(Initial Stage) Every detector (D_i) that establishes interactions longer than a threshold time - τ_{neg}, $\tau_{neg}\in\mathbb{N}$- is eliminated and replaced by another arbitrary detector (D'_i) such that $T_{D_i}=T_{D'_i}\wedge k_{D_i}=k_{D'_i}\wedge L_{D_i}=L_{D'_i}$, $R_{D'_i}$ is randomly drawn and $C_{D'_i}$ is changed accordingly.*

According to the ligands displayed by the presenters during the education process it is possible to define ligands that belong to the system, called self ligands (S), and ligands that do not, called nonself ligands ($\overline{S}$). The ligands space (L_S) is composed by the self and nonself ligands, such that $L_S = S \cup \overline{S}$ and $S \cap \overline{S}=\emptyset$.

During the education process an extended repertoire of detectors is educated. This repertoire will be used in the surveillance of anomalies in the later detection stage, after the education process. The educated repertoire of detectors can be defined as follows:

Definition 7. ***Educated Repertoire of Detectors*** *The educated repertoire of detectors is composed by an arbitrary number of educated populations of detectors - N_{pops} with $N_{pops}\in\mathbb{N}$, selected during the education process.*

After the education process, the CFS is prepared to start the monitoring stage with the extended repertoire of detectors. Anergy ensures that during the dynamics of the monitoring stage the surveillance of the systems is performed by a set of N_D detectors chosen arbitrarily from the extended repertoire of detectors. The anergy mechanism is defined as follows:

Definition 8. ***Anergy*** *Every time a detector, D_i, establishes with a presenter an interaction longer than the anergy time- τ_{an} - it is replaced by another equivalent detector from the repertoire of educated detectors (D_i') with $T_{D_i}=T_{D_i'} \wedge k_{D_i}=k_{D_i'} \wedge L_{D_i}=L_{D_i'} \wedge R_i \neq R_{i'} \wedge C_{D_i}=C_{D_i'}$.*

Each detector has a subset with N_{pops} elements of equivalent detectors with equal type, connectivity, ligand, and connectivity list, but different receptors. The anergy mechanism ensures that only the most frustrated detectors are kept in the system, and that the dynamics of the system is maximally frustrated regardless of the detectors that are in the system in each iteration.

During the frustrated dynamics, the number of conjugations lasting longer than τ is denoted $c^o_{i,>\tau}$ for a population in the absence of pathogen(after the education stage) and $c_{i,>\tau}$ in the detection stage. The frequency of conjugations after W iterations, can then be obtained from $f^o_{i,>\tau}=c^o_{i,>\tau}/\mathrm{W}$ and $f_{i,>\tau}=c_{i,>\tau}/\mathrm{W}$ for both cases. The detection ratio can be defined as:

$$\mathcal{R}_i = \frac{f_{i,>\tau}}{f^o_{i,>\tau} \times F} \tag{2.8}$$

in which F is a tolerance parameter defined per presenter, such that F$\in]1, +\infty[$, which allows detection to be done with perfect tolerance. Typically F=1.2. Every time this ratio is greater than 1, it will be possible to distinguish presenters bearing a foreign ligand from those that do not, depending on the rate of long encounters. In the Figures of the following chapter presenting results from simulations, we will be interested in calculating the number of presenters for which $\mathcal{R}\geq 1$, which will be represented as R$\geq$1.

If the rate of long contacts exceeds a threshold, it is possible to up-regulate costimulatory molecules, and activate any further detector performing a long contact with that presenter.

In the next section the algorithmic implementation of this model will be discussed.

2.3.2 Model Algorithm

The complex system to protect generates data that will be used in the computational system for anomaly detection. This is an agent based-model which is divided into 2 main phases: the repertoire education and the monitoring phase. Within the monitoring phase two different stages are considered: the calibration and the detection stage (Figure 2.5). Different stopping criteria are defined so that the system changes from one stage to the next or generates a given output.

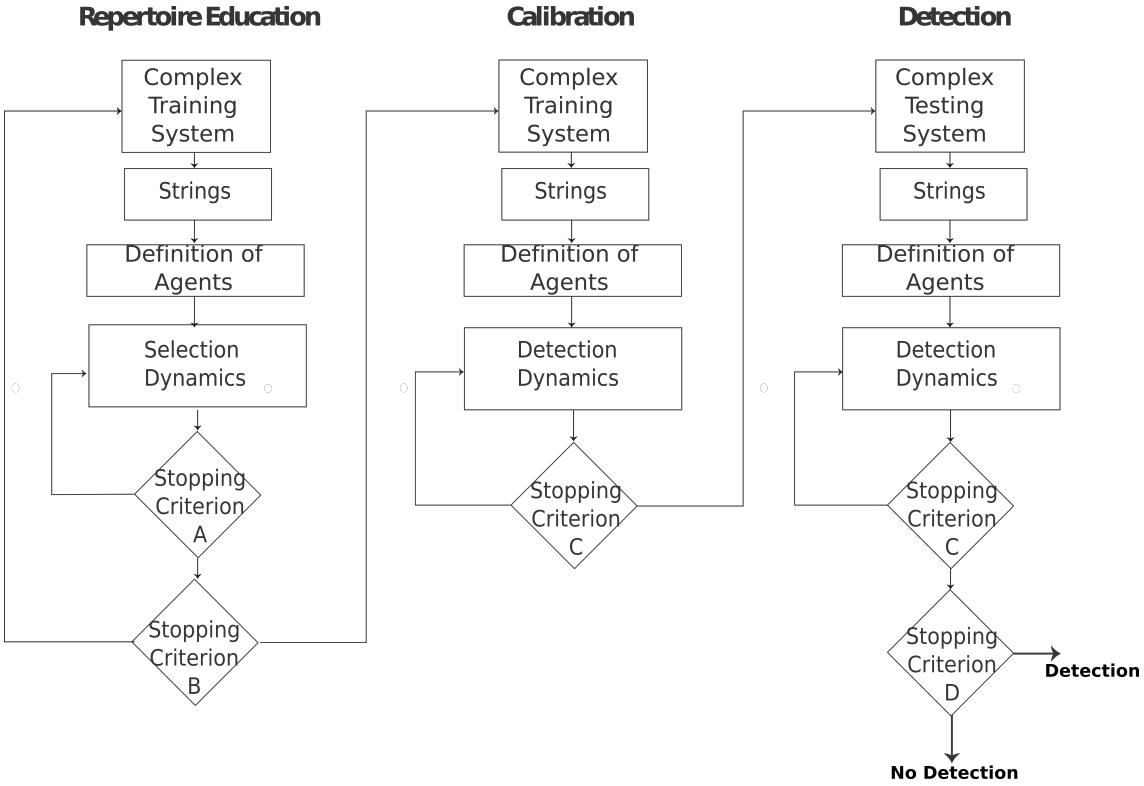


Figure 2.5: Flowchart displaying the main steps in the algorithm. During repertoire education, education process is applied until a pre-defined Threshold (Stopping Criterion A); several repertoires can be educated if necessary (Stopping Criterion B); the calibration and detection stages apply the frustrated dynamics for W iterations (Stopping Criterion C); if a presenter agent exceeds a number given of long contacts, detection is signaled for the present repertoire (Stopping Criterion D).

All the stages have very similar structures in the algorithm. They are initiated with the codification of the information of the complex system into sequences to be used in the definition of the agents. However, different information is used in the 3 stages. The set of data which characterizes the normal behavior of the complex system is utilized in the first two stages, while the data that need to be tested are used in the detection stage. Also the dynamics that is generated is similar in

repertoire education, calibration and detection stages. Here, the difference is that in the detectors selection, the dynamics comprises a selection process while the detection dynamics comprises the anergy process.

During the education stage, the educated repertoire of detectors is selected to frustrate maximally the dynamics. The repertoire is composed by N_{pops} sets of educated detectors, one population is generated in each passage by stopping criterion A. The education process stops when all the N_{pops} populations are educated - stopping criterion B is then satisfied.

After the education stage, the monitoring phase is divided into calibration and detection stages. During the calibration stage, the normal profile in the frequency of the conjugation lifetimes is established through a detection dynamics for each presenter - $f^{o}_{i,>\tau}$. The establishment of the normal profile of the conjugations dictates the end of this phase - stopping criterion C is fulfilled.

The last stage of the algorithm is the detection stage. In this stage it is evaluated if the frequency of the conjugation lifetimes changes or not with presenter agents through the sequences which encode the complex system operation that is being tested. After this evaluation, stopping criterion C is accomplished. Then, a detection or a no-detection is signaled in the end of the detection stage - stopping criterion D.

In order to understand the algorithm and the model in general, the selection and detection dynamics will be detailed in the next subsection, followed by the definition of the detection or no-detection signaling.

2.3.2.1 Selection or Detection Dynamics

The algorithm distinguishes two dynamics: the education and the detection dynamics. All stages have a common algorithm that generates the same dynamics which is independent of the stage. The common dynamics algorithm has the generic pseudocode presented below (Figure 2.6).

From one iteration to the next, a random permutation of all the presenters and all the detectors is generated. This random permutation avoids giving priority to any of the agents in the system. Each position of the permutation originates an interaction between the agent in this position of permutation, A_i, and another random agent selected within the first agent's list of connectivity, A_j. Per iteration, each agent has, at least, one chance of optimizing with an arbitrary agent of its connectivity list. Actually, on average, each agent has not one but two opportunities to optimize per each iteration: one chance due to the random permutation, A_i, and another

```
1  for(iteration=1; iteration<=Max_iterations; iteration++)
2  {
3   Generate a random permutation of all the agents;
4       for(i=1; i<=N; i++)
5       {
6        Definition of the agent A_i, in position i of permutation(A);
7        Possibility of dissociation (A_i,conjugate[A_i]);
8        Selection of a random agent A_j from ai list of connectivity;
9         Possibility of dissociation (A_j, conjugate[A_j]);
10       if (conjugate[A_i]! = A_j AND A_i, A_j are favoured by the interaction)
11            {Save the conjugation lifetime(A_i,conjugate[A_i]) or the
                                                        no-conjugated lifetime;
12             Save the conjugation lifetime(A_j,conjugate[A_j]) or the
                                                        no-conjugated lifetime;
13             Formation of the conjugation A_i, A_j;
14            }
15       end if
16       if (conjugate[A_i]! = A_j AND A_i, A_j are not favoured by the interaction)
17            {Verification of the conjugation lifetime of (A_i, conjugate[A_i]) and
                                                        (A_j, conjugate[A_j]);
18             if(Lifetime(A_i, conjugate[A_i]) OR (A_j, conjugate[A_j])> =τ_neg)
19              {Education(A_i, conjugate[A_i] OR A_j, conjugate[A_j])
20                          OR Anergy(A_i, conjugate[A_i] OR A_j, conjugate[A_j]);
21              }
22             end if
23            }
24       end if
25       if (conjugate[A_i] = A_j)
26            {Verification of the conjugation lifetime of A_i, A_j;
27             if (Lifetime(A_i, A_j)> =τ_neg)
28              {Education(A_i, conjugate[A_i] OR A_j, conjugate[A_j])
29                          OR Anergy(A_i, conjugate[A_i] OR A_j, conjugate[A_j]);
30              }
31             end if
32            }
33       end if
34       if (A_i is alone AND Education Stage)
35            {Verification of A_i no-conjugated lifetimes;
36             if (no-conjugated lifetime(A_i)> =τ_pos)
37              {Education(A_i);
38              }
39             end if
40            }
41       end if
42      }
43      end for
44  }
45 end for
```

Figure 2.6: Pseudocode used for the models in this thesis. For simplicity the outcomes of Education and Anergy are not presented.

because a random agent A_j is selected to interact with A_i.

A new conjugation (A_i, A_j) is initiated if both agents favor that interaction. In this case, the conjugation state changes and lifetimes for conjugated and non-conjugated agents are saved. In the negative selection case, both conjugation lifetimes or non-conjugated lifetimes are checked, depending if A_i, A_j are or are not in interaction. If the conjugation or no-conjugation lifetime is equal to a threshold time, τ_{neg} or τ_{pos}, respectively, the detector is eliminated in the education stage. In the detection stage, if the conjugation lifetime is equal to a threshold time, τ_{neg}, the detector becomes anergic and is replaced by another equivalent detector. Differences in the education or in the detection dynamics are signaled education or anergy in the pseudocode, respectively. The alternative algorithms will be presented below in separate sections.

Education Algorithm

In order to simulate the negative and the positive education, a non-directional selection process was implemented. Two different selection processes operate in detectors to avoid that they stay without interacting or interact in a non-frustrated dynamics. Thus, every time a detector remains τ_{pos} iterations without interacting or τ_{neg} iterations in an interaction with the same presenter, the detector is eliminated and another arbitrary detector enters in the system. In the pseudocode in Figure 2.6 every time the education process is mentioned - lines 19, 28, 37 -, the pseudocode in Figure 2.7 is used. The line marked with * represents an alternative instruction for the negative education process.

```
1  Terminate the conjugation (Ak,conjugate[Ak]);
2  Change the conjugation state for both agents;
3  Generate a random IList for the detector;
4  Generate a random ligand for the detector*;
5  Initializate the counters for the new detector and generate the Connectivity List;
```

Figure 2.7: Pseudocode for the generation of a new detector in the education stage.

The updating of τ_{pos} and τ_{neg} values are crucial for the convergence of the education process. Although the update of these values is made in independent windows of education in a fixed number of iterations, W_{ED} - one for each threshold -, they are made in a similar way. At the beginning of the simulation both values of τ_{neg} and τ_{pos} are initiated with an arbitrary large value. After W_{ED} iterations, they are updated

to the maximal non-conjugated lifetime or to the maximal conjugation lifetime that established in W_{ED}. From here, every time an agent remains without interacting for τ_{pos} iterations or interacts for τ_{neg} iterations, the detector is eliminated and replaced by another detector or the interaction is destroyed and the detector eliminated and replaced by another detector, respectively, according to Figure 2.7.

If no detector is replaced in W_{ED} iterations in the positive or in the negative education process, the corresponding τ_{pos} or τ_{neg} values are updated in the corresponding process and the selection process starts again until a new updating is required.

The process is repeated until the value of τ_{neg} equals the τ_{ed} selected in stopping criterion A (Figure 2.5). The population of detectors is saved and the number of educated populations is increased by one.

The education of another population is initiated through a random permutation of an established number of positions of the IList (k) of each detector of the first population educated. This procedure ensures that the network of interaction established in the first population of detectors is maintained. Due the fact that the network is already established, these detectors only undergo the negative selection process. Thus, each detector originates a subset of detectors with a different IList (in the k top positions) but the same ligand, connectivity and connectivity list of the detector. After N_{pops} populations of educated detectors the stopping criterion B (Figure 2.6) is accomplished and the repertoire education process finishes.

Anergy Algorithm

After the education the repertoire of educated detectors has been selected. During the calibration and the detection stages, every time a detector is left alone after an interaction with a lifetime longer than the anergy time, τ_{AN}, it becomes unresponsive or anergic and it is replaced by another equivalent detector from an arbitrary educated population between 1 and N_{pops}. The new detector has the same network of interactions, but a different IList - although all the ligands are the same. The pseudocode for the anergy of the detectors is presented in Figure 2.8.

Due to anergy, the composition of the detectors' population is continuously changing, which ensures that the surveillance of the system is maintained by the extended repertoire of detectors. In addition, anergy also reduces the number of false positive activations, because it prevents wrong activations caused by poorly

```
1 Terminate the conjugation (A_k,conjugate[A_k]);
2 Regist the conjugation lifetime for A_k and conjugate[A_k];
3 Change the conjugation state for both agents;
4 Generate a random population p between 1 and N_pops;
5 Replace the IList of the detector for its ILists in population p;
```

Figure 2.8: Pseudocode for the anergy in the detection stage.

educated detectors.

2.3.3 Model Concepts

According to the main definitions presented before, a generic CFSs , in which presenters and detectors are shown, is represented in Figure 2.9. The diversity in the ligands of presenters is arbitrarily large, L_6, L_2,...,L_9, while the receptors are less diverse. There are as many ligands in the presenters as the number of the sequences that are necessary to code the "normal" behavior of the complex system. The receptors in presenters are defined according to the ligand of the detectors for which each presenter has maximal affinity with - here, only two different ligands are displayed by detectors. All presenters within the same subtype have a common receptor. This classification of the detectors in one or another subtype (or cluster) can correspond, for example, to the expression or not of a molecule on the cells' surface.

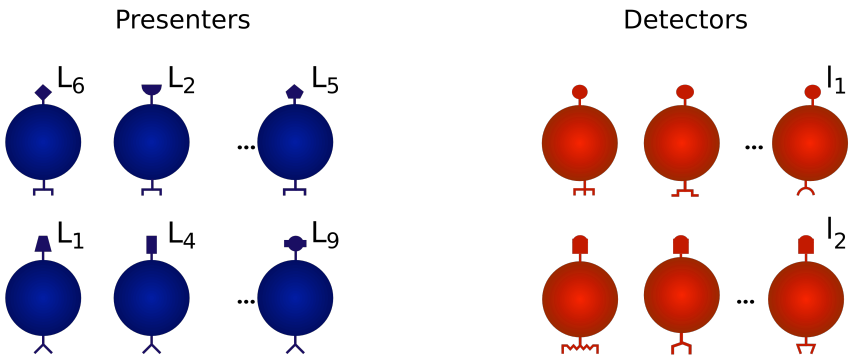


Figure 2.9: A simple model with two agent types, presenters and detectors, and with two subtypes in each. The diversity of ligands displayed by the presenters is arbitrarily large, while their receptors are less diverse: all presenters within the same subtype have the same receptor. On the contrary, detectors have a small ligands diversity but arbitrarily large receptors diversity.

On the contrary, detectors have a small diversity in ligands which is dependent on the ligand that each detector presents. In the system considered, only two different ligands are presented - l_1 and l_2. Detectors are extremely cross-reactive which allows them to recognize all the ligands displayed in the system. One within all the possible approaches to model the diversity in the receptor of the agents is to define an interaction list (IList) in which all the ligands of the opposite type are placed in decreasing order of affinity.

Presenters and detectors engage in a frustrated dynamics in which all the agents are continuously trying to optimize the ligand they interact with. Each agent favors

interactions with agents that are in top positions of their ILists and it changes pairing every time a preferred agent appears.

2.3.3.1 Dimensionality of Ligand's Space

The definition of the size of the space is important in CFSs because it will affect the functioning of the anomaly detection system. To illustrate this, Figure 2.10 shows binary information extracted from a complex system which will be coded into sequences using a different number of bits ($NBits$). The number of bits considered defines the size of the ligand's space that is obtained by the expression 2^{NBits}.

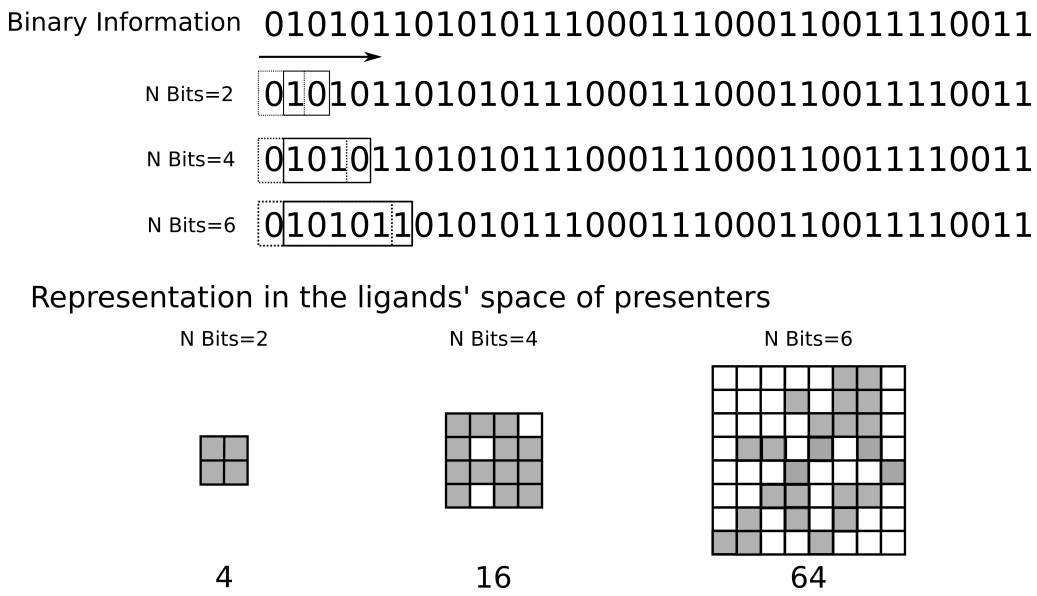


Figure 2.10: Binary information extracted from a complex system can be coded into sequences using sequences with a different number of bits, $NBits$. The number of bits considered defines the size of the sequences' space. For $NBits = 2$, all the 4 ligands are self patterns. If the same binary information is coded into sequences of 6 bits, 24 different sequences will be generated from out of the 64 possible ones.

An example of a system in which all ligands are self is the one with $NBits = 2$. Here, the binary information is coded in sequences with 2 bits, which means that all the 4 ligands are self patterns. In systems with ligands in small dimensional spaces, all the ligands are needed to characterize the normal behavior of the complex system: L_S = S and $\overline{S}$=$\emptyset$.

The increase in the number of bits used to code the same binary information increases the size of the space and, consequently, the number of different ligands used. If the same binary information is coded into sequences of 6 bits, 24 different

sequences will be originated from 64 available ones. The normal behavior is coded with a small fraction of the space, as there are ligands that are not used. Increasing the space dimension further almost all ligands become distinctive and the number of nonself ligands is much larger than the number of self ligands.

The selection of the right size will ensure a proper monitoring of the complex system. The intrusion detection is not possible with $NBits = 2$ due to the fact that there are no foreign ligands available to display by presenters - all the ligands are self. Thus, only self perturbations can be detected in this case at most. This shows that $Nbits = 2$ is an insufficient space to code the binary information presented. In the case of considering systems with $NBits = 6$ anomalies can be due to intrusion or due to homeostatic perturbations. However, the selection of a higher space dimension also have implications in the CFSs.

In CFSs the dimension of the space has implications in the size of the ILists which code the receptor of the detectors. The ILists order all the ligands in the space, so that there are $64! = 1.27 \times 10^{89}$ available ILists in the system with $NBits = 6$. Due to the fact that in educated systems ILists are randomly generated, the increase in the space size increases exponentially the number of possible ILists that are available for detectors.

The approach based on the ILists seems to have serious limitations due to the increase of the size of the space. However, they can be seen as a mathematical function that for a given input (the ligand) gives an output value (an affinity measure). Moreover, different approaches to compress the information contained in the ILists were already developed in parallel, with the same results obtained for systems in which the ILists are implemented [29, 30]. Several strategies will be discussed to select the detectors' ILists that maximally frustrate the dynamics of the system, independently of the size of the space and the huge diversity generated for the detectors' receptors. How the whole diversity in detectors ILists is generated will be the issue of the next section.

2.3.3.2 Diversity in the receptors of detectors.

The T Cell Receptor (TCR) serves a critical role in the differentiation, survival, and function of T cells, and its triggering elicits a complex set of biological responses that protects the organism from infectious agents [31–33]. The formation of TCR is made using an assembly process with the combination of gene segments in each T cell. This gene rearrangement is the process responsible for the diversity in the

recognition of all the potential diversity of the antigens [34].

To better understand how this diversity can be generated with a finite number of genes, the formation of the TCR is compared with the construction of sentences with a finite number of possible words or groups of words, which represent the gene fragments (adapted from [35]). Words are placed in 3 different groups that correspond to the different groups of genes - constant, diversity and joining gene segments - represented as Blocks 1, 2 and 3 .

Block 1	Block 2	Block 3
The Sun	Shines	Light
The Moon	Reflects	Water
The Star	Is	Red

Some resulting "TCR combinations"
The Moon reflects light
The Sun is red
The Star shines water

This generation process ensures that in the immune system around 10^7 possible TCRs could be generated [17]. This number can be increased to 10^{16} possible TCRs when junctional diversity is considered. The diversity in the generation of TCR structures is also considered in the CFSs.

Each detector has a receptor whose information is coded in a IList that orders all the possible ligands in an arbitrary decreasing order of affinities. This is randomly generated for each detector. No restrictions on possible ILists are taken - all receptors are equiprobable -, so diversity of ILists is also huge - N_{REC}=1.27x10^{89} possible receptors can be defined with 64 different ligands. An increase in the size of the space increases exponentially the diversity of the receptors that can be generated.

Because all receptors are equiprobable, the probability of different detectors having the same receptor is negligible. Thus, each detector senses differently all the ligands displayed by presenters, which means that different detectors establish interactions with different affinities with the same ligand due to the differences in ILists.

2.3.3.3 Detectors Selection

Goal of the education process

In immunology, it is accepted that thymocytes undergo a selection process called repertoire education in which T cells are selected according to their affinity for the peptide-MHC complex displayed by the APC. Thymocytes that have low affinity for the ligand presented in the thymus are eliminated by neglect. The remaining positively selected lymphocytes recognize antigens displayed by self MHC molecules [1, 17]. Within the positively selected set, thymocytes that strongly recognize self antigens are negatively selected and are prevented from completing their maturation, thus eliminating cells that would potentially react in harmful ways against self tissues (Figure 2.11) [36, 37].

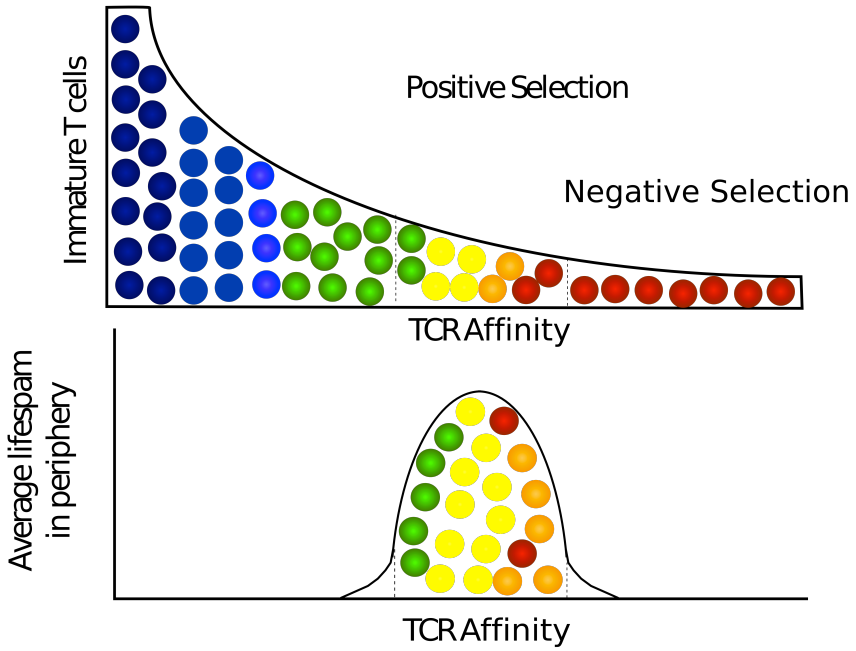


Figure 2.11: Detectors' selection process based on their receptors affinity [37]. TCRs having higher or lower affinity towards antigens displayed by self MHC are eliminated. Only detectors with intermediate affinities are selected - represented in the figure between the 2 dash lines.

Figure 2.11 illustrates the process of detectors' selection based on their affinity. TCRs having higher or lower affinity towards antigens displayed by self MHC are eliminated. Only the detectors with intermediate affinity are selected. According to

this immunological view, T cells emerging from the education process should have an optimal affinity range for antigens displayed by self MHC molecules to ensure "normal immune homeostasis" (Figure 2.12)[38, 39]. Mistakes in affinity strengths between T cells and self antigens are related with immune deficiencies or autoimmune diseases. Ideally, T cells should have moderate reactivity against self and nonself to ensure detection against foreign peptides and in total respect of self.

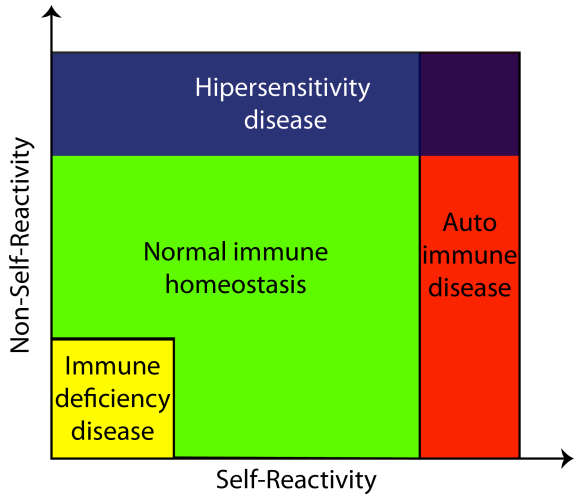


Figure 2.12: Dependence between self-reactivity and non-self-reactivity after the education process and associated diseases [38]. According to this immunological view, T cells emerging from the education process should have an optimal affinity range for antigens. Mistakes in affinity strengths between T cells and self antigens are related with immune deficiencies or autoimmune diseases.

In CFSs, detectors should also be selected, so that only those maximizing the frustration are chosen. On the one hand, it is necessary to select only detectors that are able to interact with presenters, by positive selection. The positive education in CFSs ensures that all detectors are able to interact frequently with presenters. On the other hand, it is necessary to eliminate detectors that can not engage in a frustrated dynamics, by negative selection. The main concern about the negative education process in CFSs is not shaping the affinity value with which detectors recognize ligands displayed by presenters, but to increase the frustration of the interactions between detectors and presenters. Detectors interact with presenters with maximal affinity if they are in a frustrated dynamics. In this case, there will always be agents capable of destroying these conjugations, and no response will be triggered.

The perspective of the negative education process in CFSs is one of the main differences concerning the immunological view. While the conventional view assumes

that all detectors have affinities around a given value, in CFSs detectors can have maximal affinity for all the possible ligands displayed by presenters, that can frustrate the dynamics. The task of the education process is to ensure that all presenters and all detectors interact in interactions with minimal lifetimes.

Complexity of the education process

The selection of the repertoire of detectors that frustrate the presenters dynamics is not easy. Firstly, there is a huge diversity of possible receptors that are generated even for small number of ligands, due to the random generation of the receptors. This diversity increases the difficulty of the process. Secondly, the selection of detectors depends also on the remaining detectors in the system. The presence or the absence of some detectors can dictate the selection of some detectors and elimination of others: the education process depends on the context.

Concerning the diversity of ILists, for instance, in a space with sequences of 6 bits, each detector has an IList within 1.27×10^{89} possibilities, which is an enormous diversity. Within all the possible ILists the education process should converge to form a set of ILists that allow the detectors to interact with a frustrated dynamics with maximal interactivity and minimal interaction lifetimes.

In addition to the diversity available in the ILists, another mechanism contributes to intricate the process. The selection of detectors is made in context, which means that the presence or the absence of some detectors can dictate the selection of some among all possible ones. Although detectors do not interact directly, different dynamics between presenters and detectors can be generated such that some detectors can not be accepted in consecutive interactions or form a stable conjugation. Because of that, some detectors that have ILists that frustrate the system can be eliminated by others.

After the education process, the selected detectors will be engaged in a frustrated dynamics. Although the maximal affinity of the interactions is maintained, the ordering of the ILists ensures that agents have in their top positions ligands of the agents of the opposite type which have minimal affinity for the first ones. Actually, the complete ordering of the ILists of the detectors is impossible even for small systems; what is really crucial is that the top positions of ILists are educated. Thus, reduced connectivities are considered in systems with larger space sizes during the education process - despite the fact that ILists place all the ligands with which the

detector can potentially interact. The connectivity of the detectors will be the issue of the next section.

2.3.3.4 Connectivity

It is not completely clear if T Cells can potentially interact with all the self peptides presented in the Thymus or if there is a restriction related with, for example, an affinity threshold or a spacial limitation that prevents some interactions. In Immunology both assumptions can be more check work and, in CFSs they are both relevant. The first approach considers that there is a threshold in the affinity value below which detectors do not interact. In this case, each detector interacts with the same number of different ligands which corresponds to a fixed range in the IList. It is also possible to consider that during the education process, detectors interact with a limited number of presenters that surround them.

To illustrate both approaches, let us consider that each detector has a restricted connectivity equal to 3. Figure 2.13 represents ILists with arbitrary ligands together with the representation in the presenters' ligands' space. The shaded areas in the ligands' space represent the interaction spaces that six arbitrary detectors cover in their interactions. With a cross "x" different ligands are represented.

One of the approaches assumes that all detectors can only interact with the top 3 positions in a IList (Figure 2.13A). Potentially detectors interact with all these ligands, regardless of the fact they are displayed by presenters or not and regardless of the number of presenters displaying them. Bearing the same connectivity value in mind, in the other approach, each detector interacts with 3 presenters, despite the fact that 1, 2 or 3 different ligands were presented(Figure 2.13B). In case each presenter displays a different ligand and all the ligands are in the system, both definitions are equal.

In this work the first approach is considered. There is a value of affinity equal for all the detectors that ensures that each detector interacts with the same number of different ligands. The restricted connectivity per detector is the mechanism responsible for the scalability of the education process, independently of the size of the system considered, as it will be demonstrated in the numerical results presented later. The affinity between agents in CFSs is determined by the ILists of the agents and it is responsible for the dynamics of the conjugations established. In the next section, affinity will be discussed in the light of CFS.

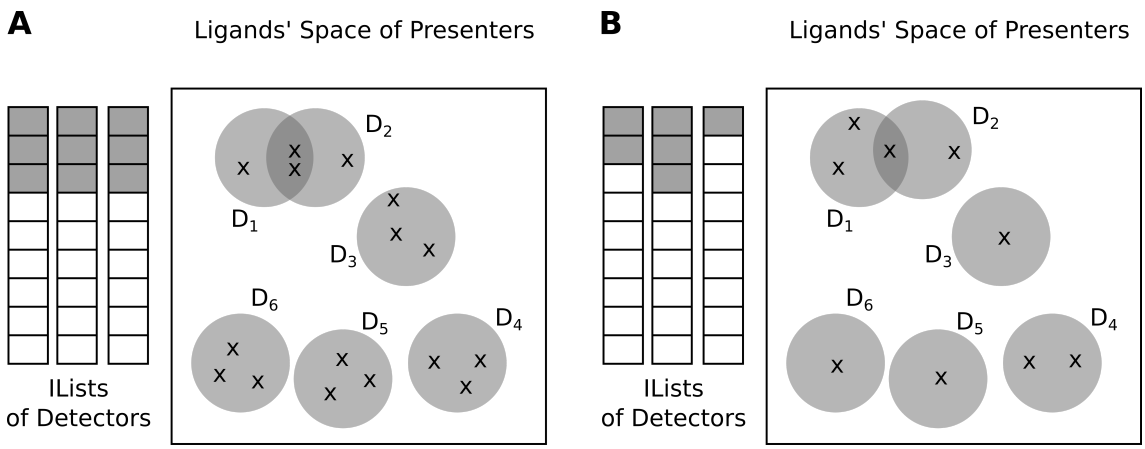


Figure 2.13: Representation of the interaction area covered by ILists of 6 detectors (D_1,...,D_6) based on ligands (A) or on agents (B) in the ligands' space of presenters. Different ligands are represented with a cross "x". (A) There is a threshold in the affinity value below which detectors do not interact and establishing the grey regions. In this case, each detector interacts with the same number of ligands which corresponds to a fixed range in the IList - 3 top positions. Detectors interact with all these ligands, regardless of the fact that they are displayed by presenters or not and regardless of the number of presenters displaying them. (B) In this other approach, detectors interact with a limited number of presenters surrounding them, despite the fact that 1, 2 or 3 different ligands were presented by these 3 presenters.

2.3.3.5 Affinity of Interactions

In the context of CFSs agents interact with maximal affinity with agents placed in the top position of their ILists. Maximal affinity is not a problem in CFSs, as it is in other models described in the literature, in which the affinity of the interactions needs to be reduced to ensure perfect tolerance towards the elements of the system.

In CFSs agents can interact with maximal affinity, as long as the dynamics is frustrated. In this case, every time an agent interacts with maximal affinity with another, the second one should interact with minimal affinity with the former. The interaction is bidirectional and each direction - from presenter to detector or from detector to presenter - has an affinity that depends on the position on the ILists. The affinity D_1-P_1 is determined by the position of the ligand of D_1 in the IList of P_1. On the other hand, the affinity P_1-D_1 is determined by the position of the ligand of P_1 in the IList of D_1, as presented in Figure 2.14, for 2 different cases.

The stability of the interaction is low when the affinity in one direction is maximal and in the other, minimal, because one of the agents is very dissatisfied and it easily finds an agent displaying a ligand placed higher in its IList. The stability of the

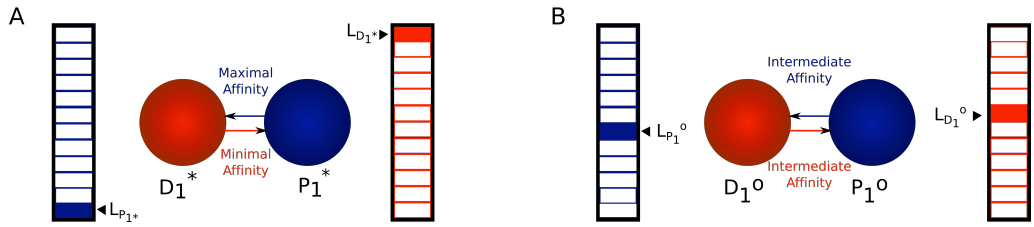


Figure 2.14: Affinity of interactions in a CFS. In a CFS, interactions are bidirectional and interactions on each direction - from presenter to detector or from detector to presenter - have an associated affinity that depends on the position of the ligand displayed by the opposite agent on its IList. The affinity in the interaction D_1-P_1 is determined by the position of the ligand displayed by D_1 in the P_1 IList. On the other hand, the affinity in the interaction P_1-D_1 is determined by the position of the ligand of P_1 in the IList of D_1. (A) The stability of the interaction is low when the affinity in one direction is maximal and in the other, minimal, because one of the agents is very dissatisfied (D_1^*) and it easily finds an agent displaying a ligand placed higher in its IList. (B) The stability of the interaction is higher for agents displaying ligands with intermediate affinities in both directions because in both cases preferences are fairly satisfied (D_1^o and P_1^o).

interaction is higher for agents displaying ligands with intermediate affinities in both directions because in both cases preferences are fairly satisfied. A more detailed model concerning the stability of the interactions and the positions of the ligands of the agents interacting in the opposite IList is presented in section 3.1.1.1.

2.3.3.6 Extended Repertoire of Educated Detectors

Throughout life, the thymus is continuously selecting T cells to generate an extended repertoire of T cells [1, 35, 40]. This process is more intense in the first years of life and it decreases with age, according to Figure 2.15 ([1], p. 45). Independently of the education process in which each individual cell was generated, T cells should cooperate in detection tasks. In addition to the task of shaping the affinity of thymocytes, the education process also needs to ensure that all T cells will behave similarly towards antigens in the periphery.

In CFSs an extended repertoire of detectors is educated to ensure that surveillance is maintained by a large number of detectors, despite the fact that only a population of N_D detectors from the extended repertoire is in the system in each iteration. This population is composed by detectors from different educated populations obtained in different moments of the education process. Thus, each com-

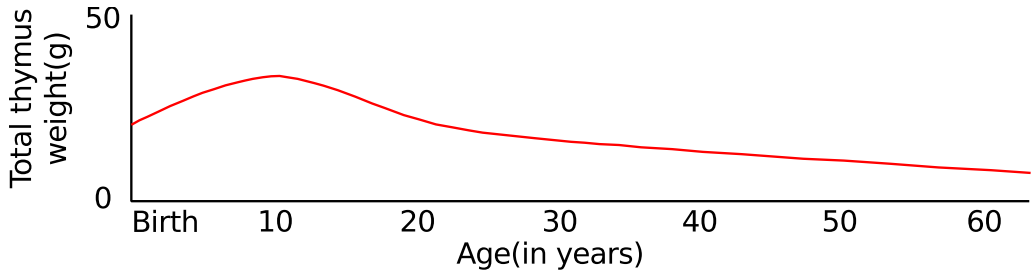


Figure 2.15: Continuous generation of T lymphocytes throughout life ([1], p. 45). This process is more intense in the first years of life and it decreases with age.

position of the detectors within a detectors' population should perform a frustrated dynamics, in every iteration, regardless of the educated population in which each detector was selected.

2.3.3.7 Anergy and Costimulation

The role of anergy and of costimulation in the immune system is not completely clear. The receptor of the T cell engaged with antigenic peptide-MHC may induce activation or clonal anergy with the presence or absence of the costimulatory signal, respectively [1, 41–44].

In CFSs it is assumed that every time a detector establishes an interaction longer than a characteristic lifetime, called anergy time τ_{an}, the detector becomes unresponsive or anergic and it is replaced by an equivalent one from the repertoire of educated detectors.

The anergy mechanism has a double effect on the dynamics. On the one hand, it ensures that only the more frustrated detectors remain in the system - those with lifetimes below τ_{an}. With this directional selection, presenters do not perform long interactions with the same detectors twice, and, consequently, the number of wrong activations (false positive) due to detectors that do not frustrate adequately the dynamics is minimized. On the other hand, anergy ensures that an extended number of detectors maintain the surveillance of the systems. The higher the number of detectors, the higher the probability of the invader's ligand being placed in the top positions of the IList and the higher the probability that detection is accomplished.

After the education stage, presenters define the "normal" pattern of long conjugations, either in duration and in number. Every time presenters have a decrease in frustration, the engage in longer conjugations with higher frequency. This can thus up regulate costimulatory molecules signaling this decrease.

Both mechanisms are crucial to increase the accuracy of the anomaly detection system, as it will be presented in the next section.

3 Mathematical Approach

3.1 Mathematical Approach

3.1.1 Analysis of Perfect Systems

In order to gain a deeper understanding of cellular frustrated systems, mean field equations were derived and numerically integrated for the simplest set of models. For a simple first approach, a population with perfectly ordered ILists was chosen. The system has an equal number of presenters and detectors, and each of them is divided in two subtypes - denoted as 1 and 2, respectively-, such that N_P=N_{P_1}+N_{P_2} with N_{P_1}=N_{P_2}, and N_D=N_{D_1}+N_{D_2} also with N_{D_1}=N_{D_2}. The total number of agents is given by N=N_P+N_D. A schematic representation of the system is shown in Figure 3.1. On the left are represented presenter agents. They have very diverse ligands, denoted by L_i, with i being the agent index. All presenters of a given subtype have the same receptor and consequently the same IList. Detectors have considerable diversity in their receptors. This is encoded in their ILists, different for each detector. In this, simple first model, detectors ILists follow a well defined order. First all subtype I detectors have on the top half positions of their ILists, subtype II ligands and on the bottom, subtype I ligands.

For this system it is possible to define the normalized frequencies conjugations involving subtype i presenter agents and subtype j detector agents by $n_{P_iD_j}$=$N_{P_iD_j}$/N; i, j=1,2, as well as the frequencies of the non-conjugated agents, $n_{P_{i\phi}}$=$N_{P_{i\phi}}$/N, i=1, 2 or $n_{D_{i\phi}}$=$N_{D_{i\phi}}$/N, i=1, 2. The dynamical evolution of these frequencies can be obtained deriving mean field rate equations for each frequency. These have to account for all contributions leading to the formation and destruction of each species, i.e., either pairs of conjugated or non conjugated agents. For conjugates involving subtype

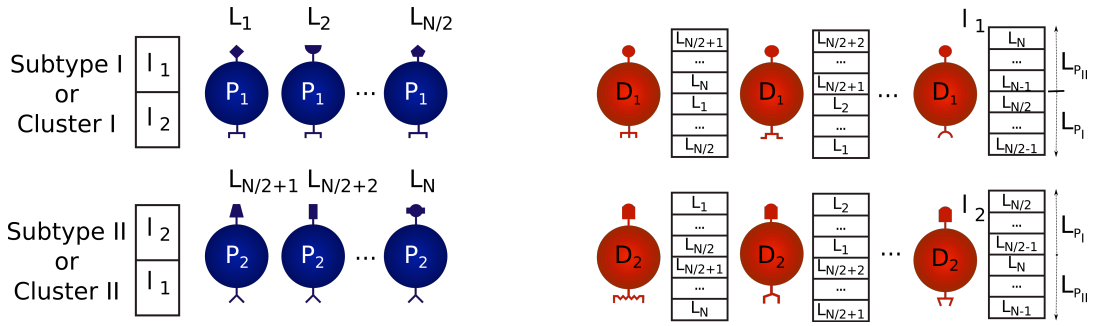


Figure 3.1: Representation of a simple model with perfectly ordered ILists. The model considers two agent types, presenters and detectors. Presenters display all different ligands, L_1, ..., L_N, but have only two possible receptors. These correspond to only two different ILists. On the contrary, detectors have only two possible ligands, l_1 and l_2, but can have very diverse receptors. In this model all detectors have a different ILists. To make the analysis simpler, their ILists follow the predefined order indicated in the figure.

I presenter agents, P_1 and subtype I detectors, D_1, P_1D_1, all the contributions are represented in Figure 3.2. On average, when detectors interact with agents of the same subtype, they encounter a ligand placed higher in their ILists with probability p.

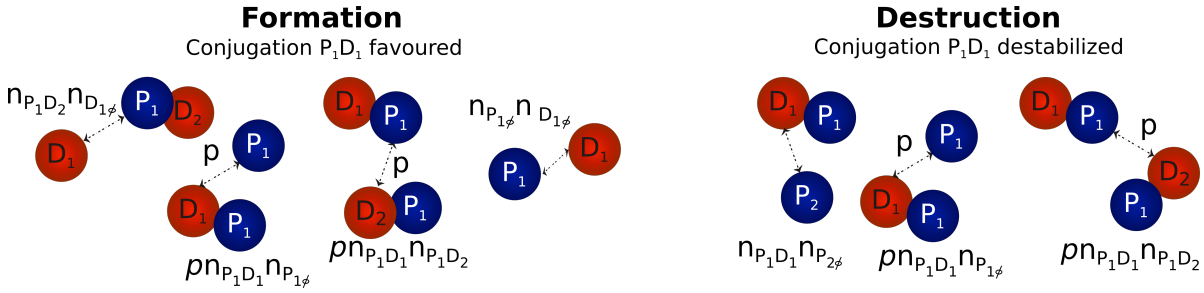


Figure 3.2: Formation and Destruction of conjugate P_1D_1, involving subtype I presenter agents, P_1 and subtype I detectors, D_1. On the left are represented all interactions that can form a new P_1D_1 conjugate. On the right are represented all interactions that contribute negatively in the first equation (Equations 3.1).

The evolution of the normalized frequencies follows the equations:

$$
\begin{aligned}
\frac{dn_{P_1D_1}}{dt} &= n_{P_{1\phi}}n_{D_{1\phi}} + n_{D_{1\phi}}n_{P_1D_2} + pn_{P_{1\phi}}n_{P_1D_1} + pn_{P_1D_1}n_{P_1D_2} - n_{P_1D_1}(\\
&\quad pn_{P_{1\phi}} + n_{P_{2\phi}} + pn_{P_1D_2}) \\
\frac{dn_{P_1D_2}}{dt} &= n_{P_{1\phi}}(n_{D_{2\phi}} + n_{P_2D_2} + pn_{P_1D_2}) - n_{P_1D_2}(n_{D_{1\phi}} + pn_{P_1D_1} + pn_{P_{1\phi}}) \\
\frac{dn_{P_{1\phi}}}{dt} &= n_{P_1D_1}(pn_{P_{1\phi}} + n_{P_{2\phi}} + pn_{P_1D_2}) + pn_{P_1D_2}n_{P_{1\phi}} - n_{P_{1\phi}}(n_{D_{1\phi}} + n_{D_{2\phi}} \\
&\quad + pn_{P_1D_1} + n_{P_2D_2} + pn_{P_1D_2}) \\
\frac{dn_{D1\phi}}{dt} &= n_{P_2D_1}n_{D_{2\phi}} + pn_{P_2D_1}n_{P_2D_2} - n_{D_{1\phi}}(n_{P_{1\phi}} + n_{P_{2\phi}} + n_{P_1D_2})
\end{aligned}
\tag{3.1}
$$

The remaining equations for the other species can be obtained by using the substitution: (P_1, P_2, D_1, D_2)→(P_2, P_1, D_2, D_1). Results from both approaches are collected and represented in Figure 3.3. Lines represent results obtained from the numerical integration of the differential equations while marks correspond to results obtained from the cellular automaton. There is a good agreement between

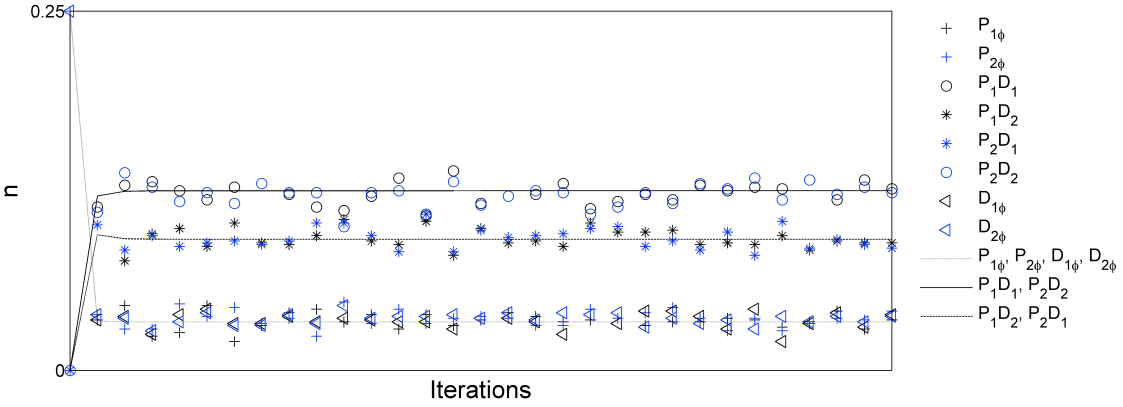


Figure 3.3: Normalized frequencies of all the species calculated by the cellular automaton (in markers) and by the integration of the mean field equations (in lines).

both approaches, which suggests that the dynamical model captures the dynamics of the cellular automaton. The frequencies obtained with the equations tend to constant values after a phase of convergence. This does not mean that the system reaches a stable configuration with all agents stably conjugated. Rather a dynamical equilibrium reached where the number of agents that change from a conjugated state to the non-conjugated state is equal to the number of agents doing the reverse. In

cellular automaton simulations, some oscillations around the steady state values can also be appreciated. This is a result of finite size effects and the stochasticity in the dynamics resulting from the random selection of the agents interacting at each time step. Another finding is that $n_{P_1D_1} = n_{P_2D_2} \geq n_{P_1D_2} = n_{P_1D_2}$. This is results from the fact that all detectors have the same ligand inside a cluster. Consequently, all detectors of the same subtype are sensed equally by presenters and consequently do not promote pair changes. The destabilization in conjugations is different for a conjugation P_1D_2 or P_1D_1, as can be understood from Figure 3.4.

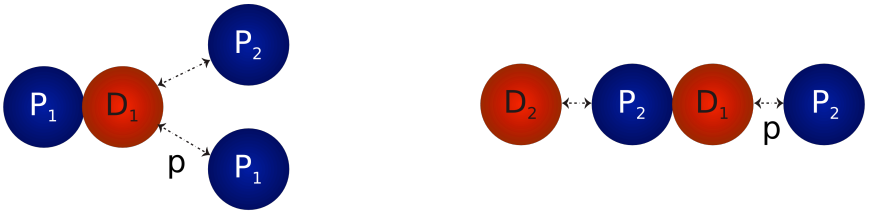


Figure 3.4: Destabilization of conjugations P_1D_1 and P_2D_1. On the left the subtype I detectors conjugated with subtype I presenters are destabilized by any subtype II presenters - destabilization with probability 1 - while this happens only with probability p for presenters of the same subtype. On the left it is shown that a P_2D_1 conjugate is destabilized with probability 1 due to interactions with subtype II detectors by the presenter agents, and it can also be destabilized with probability p due to interactions with the detector agent in the conjugate.

In both conjugations one agent is satisfied. In the conjugation P_1D_1, P_1 is satisfied. The destabilization in this case is performed only by interactions between D_1 and P_1 or P_2. In contrast, in a conjugation P_2D_1, although D_1 is satisfied, both agents can be destabilized. D_1 can optimize with a given probability among agents that belong to D_2. The presenter can be destabilized by D_2 agents.

In order to better understand the difference in the stability of the conjugations due to the positions of the ligands of presenters and detectors in the opposite ILists, a more general system with an arbitrary number of subtypes is presented in the next section.

3.1.1.1 Stability of the Interactions

To better understand the relation between the position of the ligands in the IList of the agents in interaction and the stability of the interaction, a simple model was

built. A system with 10 agents subtype was considered, with an equal number of presenters and detectors in each subtype in a maximally frustrated system. In order to simplify, it is considered that all agents belonging to the same subtype have the same ligands and receptors.

The generic equations for the conjugate P_1D_i and non-conjugated agents $P_{1\phi}$ and $D_{1\phi}$ as well as the conjugation lifetimes for a system with an arbitrary number of clusters are:

$$\begin{aligned}\frac{dn_{P_1D_i}}{dt} = {} & n_{P_1\phi}n_{D_1\phi} + \sum_{i,j=1}^{N_C}\theta(j-2)\theta(i-j)n_{P_1\phi}n_{D_iP_j} + \sum_{i,j=1}^{N_C}\theta(j-i-1)n_{D_i\phi} \\ & n_{D_jP_1} + \sum_{i,j,k=1}^{N_C}\theta(j-i-1)\theta(k-2)\theta(i-k)n_{P_1D_j}n_{D_iP_k} - \Big(\sum_{i,k=1}^{N_C}\theta(k-1) \\ & \theta(i-k-1)n_{D_k\phi}n_{P_1D_i} + \sum_{i,j,k=1}^{N_C}\theta(k-1)\theta(i-k-1)\theta(j-2)\theta(k-j) \\ & n_{P_jD_k}n_{P_1D_i} + \sum_{i,k=1}^{N_C}\theta(k-i-1)n_{P_k\phi}n_{P_1D_i} + \sum_{i,j,k=1}^{N_C}\theta(k-i-1) \\ & \theta(j-k-1)\theta(i-k)n_{P_kD_j}n_{P_1D_i} + \sum_{i,j,k=1}^{N_C}\theta(k-i-1)\theta(k-j-1) \\ & \theta(j-i-1)n_{P_kD_j}n_{P_1D_i}\Big)\end{aligned}$$

$$\begin{aligned}\frac{dn_{P_1\phi}}{dt} = {} & \sum_{i,k=1}^{N_C}\theta(k-i-1)\theta(k-2)n_{P_k\phi}n_{P_1D_i} + \Big(\sum_{j,k,i=1}^{N_C}\theta(k-i-1)\theta(k-2)\theta(i-k) \\ & \theta(j-i-1) + \sum_{j,k,i=1}^{N_C}\theta(k-i-1)\theta(k-2)\theta(k-j-1)\theta(j-i-1)\Big)n_{P_1D_i}n_{P_kD_j} \\ & - n_{P_1\phi}\Big(\sum_{i=1}^{N_C}n_{D_i\phi} + \sum_{i,k=1}^{N_C}\theta(k-2)\theta(i-k)n_{P_kD_i}\Big)\end{aligned}$$

$$\frac{dn_{D_1\phi}}{dt} = \sum_{j,k=1}^{N_C} \theta(k-j)\theta(j-2)n_{D_k\phi}n_{P_jD_1} + \Big(\sum_{j,k,i=1}^{N_C} \theta(k-i)\theta(i-2)\theta(i-k-1)$$
$$\theta(j-i-1) + \sum_{j,k,i=1}^{N_C} \theta(k-i)\theta(i-2)\theta(k-j)\theta(j-i-1)\Big)n_{P_jD_k}n_{P_iD_1}$$
$$- n_{D_1\phi}\Big(\sum_{j=1}^{N_C} n_{P_j\phi} + \sum_{j,k=1}^{N_C} \theta(j-2)\theta(k-j-1)n_{P_kD_j}$$
$$+ \sum_{j,k=1}^{N_C} \theta(k-1)\theta(j-2)n_{P_kD_j}\Big)$$

in which θ represents a discrete form of the Heaviside step function, such that

$$\theta = \begin{cases} 0, & n<0 \\ 1, & n\geq 0 \end{cases}$$

and index i represents the subtype of the detector for conjugated species and N_C is equal to the number of clusters or subtypes in the system.

The equations for the remaining species can be obtained by substitution due to the symmetry in the system. According to these conjugations, the corresponding typical lifetimes can also be obtained. Because only the stability of the interaction is analyzed, the generic $\tau^{-1}_{P_1D_i}$ for the conjugated case is given by:

$$\tau^{-1}_{P_1D_i} \sim \sum_{i,k=1}^{N_C} \theta(k-1)\theta(i-k-1)n_{D_k\phi} + \sum_{i,j,k=1}^{N_C} \theta(k-1)\theta(i-k-1)\theta(j-2)$$
$$\theta(k-j)n_{P_jD_k} + \sum_{i,k=1}^{N_C} \theta(k-i-1)n_{P_k\phi} + \sum_{i,j,k=1}^{N_C} \theta(k-i-1)\theta(j-k-1)$$
$$\theta(i-k)n_{P_kD_j} + \sum_{i,j,k=1}^{N_C} \theta(k-i-1)\theta(k-j-1)\theta(j-i-1)n_{P_kD_j}$$

The normalized lifetimes of the interaction - $\tau/\ \tau_{Max}$ in which τ_{Max} corresponds to the τ of the most stable interaction - are represented as a function of the position in the ILists for a generic agent (Figure 3.5A). The same profile of the interaction lifetimes is obtained for an arbitrary presenter of every subtype as function of the detectors' subtype (Figure 3.5B).

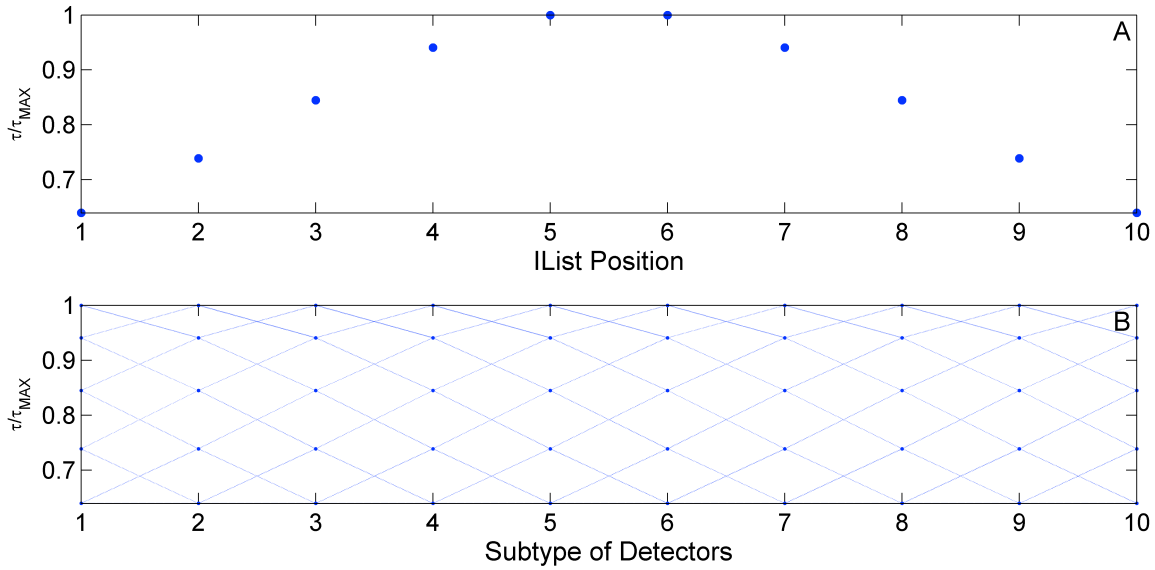


Figure 3.5: A) Normalized lifetimes of a generic agent with all the agents of the opposite type as function of its ILists positions. B) Profile of the interaction lifetimes obtained for an arbitrary presenter of every subtype as function of the detectors' subtype.

This profile changes, when an invader is introduced in the system. Its ligand appears in a random position of the detectors' ILists because it had not been presented during the education process. The strength of the interaction is higher between the invader and a number of detectors for which the invader has maximal affinity and additionally these detectors have the invader's ligand in the top positions of their ILists. Consequently, a less frustrated conjugation takes place, because both agents are satisfied in the conjugation. It is interesting to notice that this reduction of frustration naturally emerges from the frustrated dynamics in CFSs. This output is responsible for the detection of perturbations no matter the cause, as it will be shown in detail in the next sections.

3.1.2 Analysis of Educated Systems

For populations resulting from repertoire education, ILists cannot be considered to be perfectly ordered. In this case mean field-like equations can still be derived for the normalized frequencies of all the conjugated and non-conjugated agents. Three different classes of interactions can be considered:

- A conjugated detector interacts with a ligand from the same subtype as the

subtype of the ligand displayed by the presenter agent to which it is conjugated (Figure 3.6A). A probability of destabilization of p_M=0.5 was considered in these cases;

- A conjugated detector interacts with a ligand displayed by presenters that rank highly the detector agent, while the detector is conjugated to a presenter agent that rank lower the detector agent (Figure 3.6B). In this case, the education should reduced the probability that these processes destabilize the conjugate. A probability of destabilization of p_I=0.3 was considered in these cases.

- A conjugated detector interacts with a ligand displayed by presenters that rank lower the detector agent, while the detector is conjugated to a presenter agent that rank highly the detector agent (Figure 3.6C). In this case, the education should increased the probability that these processes destabilize the conjugate. A probability of destabilization of p_S=0.7 was considered in these cases.

Hence, detectors can always change from conjugate with a given probability, independently of the subtype of the presenter.

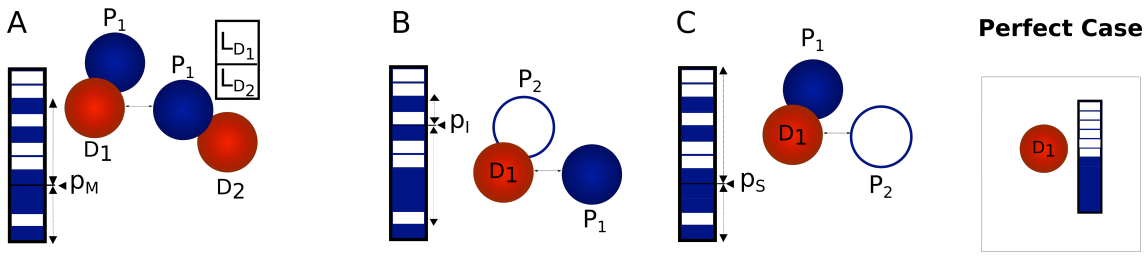


Figure 3.6: Schematic representation of the probabilities of destabilization of detectors. Three examples are illustrated in which a detector D_1 changes pair with three different probabilities. An arbitrary IList for D_1 is represented. The filled rectangles represent different ligands from subtype I, while the ones with the blue stroke represent different ligands from subtype II.

The set of mean field equations which describe the system dynamics is given by:

$$\begin{aligned}
\frac{dn_{P_1D_1}}{dt} &= n_{D_1\phi}(n_{P_1\phi} + n_{P_1D_2}) + p_I n_{P_1\phi} n_{P_2D_1} + n_{P_1D_2}(p_M n_{P_1D_1} + p_I n_{P_2D_1}) \\
&\quad p_M n_{P_1D_1} n_{P_1\phi} - n_{P_1D_1}(p_{diss} + p_M n_{P_1\phi} + p_S n_{P_{2\phi}} + p_M n_{P_1D_2}) \\
\frac{dn_{P_1D_2}}{dt} &= n_{P_1\phi} n_{D_2\phi} + n_{P_1\phi}(p_M n_{P_1D_2} + p_S n_{P_2D_2}) - n_{P_1D_2}(p_{diss} + n_{D_{1\phi}} + p_M \\
&\quad n_{P_1D_1} + 2p_I n_{P_2D_1} + p_M n_{P_{1\phi}} + p_I n_{P_{2\phi}}) \\
\frac{dn_{P_1\phi}}{dt} &= p_{diss}(n_{P_1D_1} + n_{P_1D_2}) + n_{P_1D_1}(p_M n_{P_1\phi} + p_S n_{P_2\phi} + p_M n_{P_1D_2}) + n_{P_1D_2} \\
&\quad (p_M n_{P_1\phi} + p_I n_{P_2\phi} + p_I n_{P_2D_1}) - n_{P_1\phi}(n_{D_{1\phi}} + n_{D_{2\phi}} + p_M n_{P_1D_1} \\
&\quad + p_I n_{P_2D_1} + p_M n_{P_1D_2} + p_S n_{P_2D_2}) \\
\frac{dn_{D_1\phi}}{dt} &= p_{diss}(n_{P_1D_1} + n_{P_2D_1}) + n_{P_2D_1}(n_{D_2\phi} + p_I n_{P_1D_2} + p_M n_{P_2D_2}) - n_{D_1\phi}(n_{P_1\phi} \\
&\quad + n_{P_2\phi} + n_{P_1D_2})
\end{aligned} \tag{3.2}$$

The remaining equations can be easily obtained by using symmetry operations. From the contributions for the destruction of conjugates, expressions for the characteristic lifetimes can be derived:

$$\begin{aligned}
\tau_{P_1D_1}^{-1} &\sim p_{diss} + p_M n_{P_1\phi} + p_S n_{P_{2\phi}} + p_M n_{P_1D_2} \\
\tau_{P_1D_2}^{-1} &\sim p_{diss} + n_{D_{1\phi}} + p_M n_{P_1D_1} + 2p_I n_{P_2D_1} + p_M n_{P_{1\phi}} + p_I n_{P_{2\phi}}
\end{aligned} \tag{3.3}$$

To analyze the agreement between both methods, their values were calculated in similar conditions. For the cellular automaton, the histogram characteristic lifetimes were obtained by using an exponential fitting of $P_{>\tau}$ (Figure 3.7). $P_{>\tau}$ represents the probability that a presenter i performs a conjugation that lasts longer than τ iterations and it can be mathematically defined as:

$$P_{i,>\tau} = \frac{\sum_{i=\tau}^{\tau_{MAX}} c_{i,>\tau}^{o}}{\sum_{i=1}^{\tau_{MAX}} c_{i,>\tau}^{o}} \tag{3.4}$$

in which $c_{i,>\tau}^{o}$ represents the number of conjugations lasting longer than τ iterations. The same characteristic lifetime was obtained from the mean field equations (Equations 3.3). Both approaches are compared in Table 3.1 in which the parameters of

the fittings are presented, as well as the characteristic lifetimes for each case.

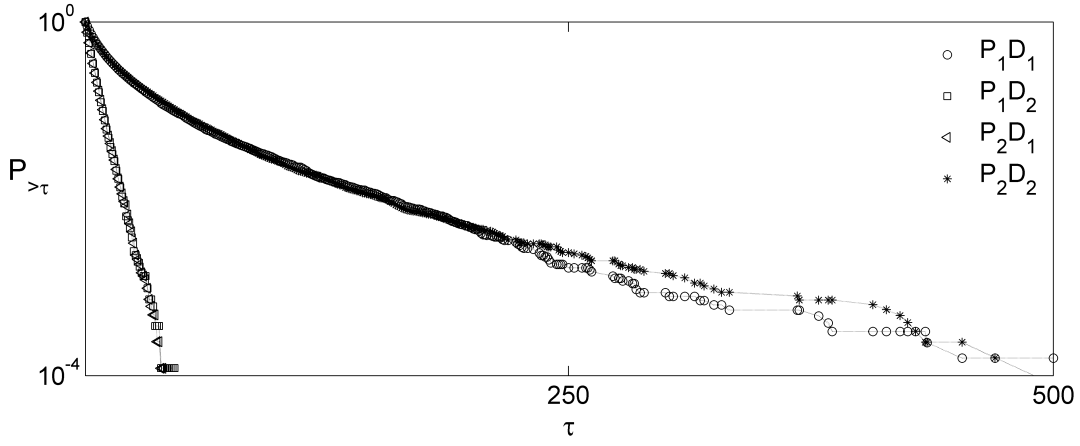


Figure 3.7: Probability of establishing conjugations lasting longer than τ iterations, $P_{>\tau}$ after the detection phase, and for pairs involving agents from the several subtypes. Conjugations involving presenters, P, from cluster i and detectors, D, from cluster j are represented as P_iD_j.

Table 3.1: Comparison between the cellular automaton (CA) and the mean field equations (MFE).

	Fitting Parameters	CA	MFE
Conjugation	$P_{>\tau}$= a $\exp^{-b\tau_C^{-1}}$	τ_C	τ_C
P_1D_1	a=0.89, b=-0.05, r^2=0.974	20.0	18.0
P_1D_2	a=1.28, b=-0.26, r^2=0.999	3.8	5.0
P_2D_1	a=1.28, b=-0.26, r^2=0.999	3.8	5.0
P_2D_2	a=0.88, b=-0.05, r^2=0.973	20.0	18.0

In spite of the imperfections in ILists due to the education process, it is possible to verify that $\tau_{P_1D_1}$=$\tau_{P_2D_2}$ and $\tau_{P_1D_2}$=$\tau_{P_2D_1}$, as expected from the previous analysis. Differences in lifetimes are due to the stochasticity in cellular automaton dynamics and the estimation of the probabilities in mean field equations. Despite the assumptions taken, the dynamics that is generated after the education process in the cellular automaton simulation agrees with the dynamics predicted by mean field equations.

4 Results

During the development of the computational system, several studies were performed in order to increase the understanding of the optimal functioning of CFSs.

It is important to keep in mind that, whereas in the computational field all the assumptions are scientifically acceptable and relevant, the same does not happen in immunology. Here, so that the assumptions are valid, they should take into account what is already known in the field about the basic mechanisms of the immune system [45, 46]. Only in this case can the results obtained by the models have relevance in the field.

In this section both perspectives are presented together although some systems are closer to applications in the computational field, while others aim at understanding the main mechanisms of the immune system in the light of the CFSs framework. Despite the relevance of the results in one or another field, all the results about the topic will be presented and discussed. The sequence of the presentation of the results follows the development of this work.

Firstly, perfect systems which, were the starting point of this work are discussed. These systems accomplish perfect self/nonself discrimination and respond to homeostatic perturbations. Their results were the clues for the development of the computational algorithm for educated systems, which were the object this work.

As in perfect systems, in educated systems a maximally frustrated dynamics should be generated for any arbitrary information presented in the sequences, such that any change in the complex system would be signaled. In order to do that, several studies concerning the education process - with the positive and the negative education - were made. The main results are described in the subsections presented next.

After the selection of the repertoire of detectors, two different types of detection

were investigated: detection of foreign ligands and detection of self perturbations (abnormal growth of some ligands and abnormal presentation of sequences). Both phenomena can originate from invader, causing a change in the normal functioning of the system, either in the computational or in the immune system. This thesis starts by the study of the capacity of detecting invaders in educated systems. Since the computational system is able to perform perfect self/nonself discrimination, the capacity of detection other types of anomalies was studied. Afterwards, the capacity of CFSs to perform detection of the change in the frequency of ligands coding the normal behavior of the system, as well as the capacity of detecting abnormal combinations of the same ligands which had already been presented, were analyzed. Finally, the capacity of generalizing presentations as legitimate or no-legitimate were tested when a small fraction of the possible presentations is displayed in the education stage. In order to be better understood, all the main results were summarized and presented in separate sections according to the different studies.

4.1 An Initial Model

The systems that will be presented here were the first systems developed in this thesis. They appeared following the previous work done in Circular Frustrated Systems - shortly described in section 2.2 - and already published [15, 20, 47]. The results obtained in these systems were very encouraging concerning intrusion detection tasks. For instance, a small number of agents is required to perform intrusion detection; the time needed to perform the task is almost the same independently of the amount of information to protect and, the most important result, the probability that an intruder escapes is almost zero and it decreases with the increase of the size of the system. Also interesting results were obtained in the detection of an abnormal growth of agents.

The circular frustrated system served as inspiration to build a system with 2 types of agents, presenters and detectors and arbitrarily large diversity. Each presenter or detector has a different ligand and receptor. Different definitions of systems could be made. Here it is assumed that $L_i = i$, independently of the type of the agent. Detectors have ILists built through the expression :

$$L_i(j) = [i + j]$$

with i equal to the ligand of the detector and j equal to the position in the IList. For the detector with i=1 and L_i=1, the first and the bottom positions are:

$$L_1(1) = [1+1] = 2$$
$$L_1(N) = [1+N] = 1$$

To maximize frustration presenters have ILists according to:

$$L_i(j) = [i + j - 1]$$

For the presenter with i=1 and L_i=1, the first and the bottom positions are:

$$L_1(1) = [1+1-1] = 1$$
$$L_1(N) = [1+N-1] = N$$

In order to better understand the structure of the ILists, their construction is represented in a simple way in Figure 4.1. The agents' ligands are represented in a circle that indicates the ordering assumed and the boundary conditions imposed. The ligands of the presenters are represented in roman numeral, while the detectors' ligands are in arabic numerals. On the sides, the IList of both agents with L_i=1 are shown. This is one among other possibilities that will in the same way originate a maximally frustrated dynamics.

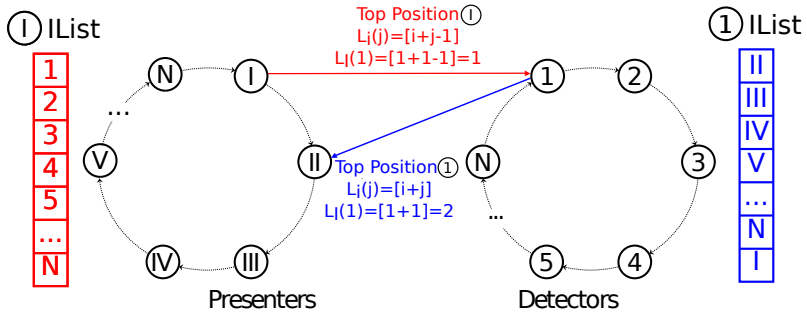


Figure 4.1: Representation of the ordering of the ILists for presenters and detectors.

The method that is required for the anomaly detection system should be as general as possible. The structure of the ILists should not be determinant in the performance of the detection system, and it should warrant that for each presentation made by presenters, detectors should be able to perform discrimination self/nonself.

These features are achieved for detection systems, in which presenters and detectors are engaged in a maximally frustrated dynamics. Thus, a negative selection

algorithm, which selects, within a set of detectors with random ILists, the ones that maximally frustrate the dynamics in the system has been developed since then. These systems are called educated systems. This was the beginning of the development of the abnormal detection system, as it is now designated.

It is interesting to notice that the main concepts that will differentiate CFSs from all the other models in the literature[48, 49] are already present in this initial approach. The agents are seen as optimization makers, which interact with different agents in order to be paired with agents for which they have maximal affinity. The selection of detectors is made based on interaction lifetimes. Each detector that exceeds the threshold of the conjugation lifetime is eliminated and another detector is introduced to replace it. The new introduced detector has an arbitrary IList that organizes all the ligands in the system in an arbitrary order. Finally, the detection is ensured by an extended repertoire of detectors that acts in sequential confined systems of detection. This first approach, which later inspired the anergy mechanism, was inspired in the real immune system, in which a network of lymph nodes promotes several different independent places of detection.

Although these systems are far from the final approach that is the object of this thesis, the results obtained in these systems justify their discussion. Thus, the results of the perfect system will be presented showing that, in a maximally frustrated system, the perfect self/nonself discrimination can be accomplished. Then these results are compared with the discrimination that is obtained in systems in which the repertoire of detectors is selected by a negative selection process.

4.1.1 Parameters and Simulations

Both systems, perfect and educated, have 2 types of agents, presenters and detectors, with 100 agents per type divided into 100 different subtypes. Each agent in the system has a different ligand and receptor. It is assumed that the ligand of each agent is equal to its subtype. Presenters in both systems have their receptors defined in the same way (Figure 4.1). The receptors of detectors are different in educated and in perfect systems. In the latter, the ILists are built with the strict order presented in the previous section, while in educated systems the ILists place all the ligands in the system in an arbitrary order.

The selection of the educated detectors that maximally frustrate the dynamics of the system is ensured by the negative selection algorithm already defined in

section 2.3.2. Nevertheless, a different stopping criterion is defined. The process ends when around 97% of the detectors are eliminated - inspired by the 97% of detectors that are eliminated in the education process in thymus [1, 2, 17] - , which corresponds to a τ_{neg}=75 and typically to around 40000 iterations in the simulations.

Detection in perfect systems is perfectly ensured by a single perfect population of detectors, as represented in Figure 4.2A. In educated systems a given number of populations was educated to be integrated in a consecutive sequence of detection systems as represented in Figure 4.2B. Here, ligands displayed by presenters are consecutively presented to different independent populations of educated detectors, represented with separated boxes in the figure, until a detection is signaled.

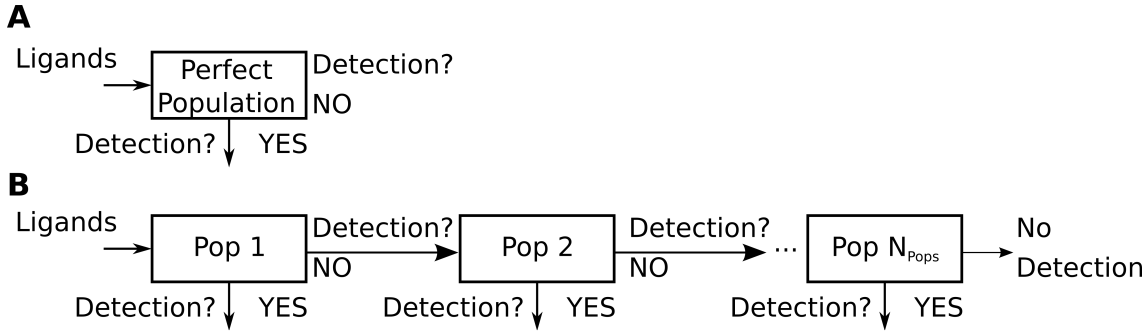


Figure 4.2: (A) Detection in perfect systems. (B) Detection scheme that uses a sequential application of different detector repertoires during intrusion detection, in educated systems.

To compare results from perfect and educated systems, the same systems were simulated. To test the performance of the intrusion detection system, N_{inv}=1000 invaders were introduced in both the perfect population or for each educated population. A detection window of W_{DET}=5000 iterations was used in simulations. To simulate the effect of introducing a non-educated ligand in the system, the foreign ligand is placed in random positions on all detectors ILists. The invader is introduced in consecutive populations of detectors until a detection is signaled. After this, a new invader is introduced and the procedure is repeated.

A detection event is triggered every time a presenter increases the frequency and the duration of the conjugations, which mathematically means that $\mathcal{R} \geq 1$, with F=1.05. All the ratios are calculated for both systems at $\tau_C = \frac{2}{3} \times \tau_{MAX}$, with τ_{MAX} equal to the maximal conjugation lifetime registered in interactions between self agents.

4.1.2 Numerical Results

4.1.2.1 Perfect Systems

Perfect systems have maximally frustrated dynamics due to the ordered structure of the ILists of presenters and detectors. To estimate the probability of failing intrusion detection in these systems, 1000 invaders were introduced in the system.

The typical histogram for the frequency of the interactions lasting longer than τ iterations is presented for the invader and for the remaining presenters in Figure 4.3A. The grey lines represent the probability of each self presenter performing an interaction that remains for at least τ iterations, while the black line marked with circles shows the same curve for the invader. It is clear from the histogram that the invader establishes consistently longer conjugations and more frequently than the remaining presenters. An interaction lifetime above which only the invader establishes interactions can be defined. This means that detection can be surgical; the response can be triggered towards the intruder without any damage to the agents of the system.

The selection of a longer lifetime conjugation to evaluate the response can be inconvenient. Longer conjugations have a small probability of occurring, as can be seen in the histogram. Thus, a detection based on short contacts is more convenient in an intrusion detection system, because these events are more likely to occur. The shortness of the lifetime to trigger responses forces that more than a single interaction should be required to initiate a response, in order to minimize false positive errors. This quantification for smaller lifetimes is captured by the ratio $\mathcal{R}$ - already defined in section 2.3.2, and calculated at τ_C. The lifetime selected to make the computation is represented by the vertical dashed line in the histogram. The detection ratios $\mathcal{R}$ are ordered and presented for all the invaders as well as the respective histogram (Figure 4.3B and C, respectively).

These results show, that as in circular frustrated systems, intrusion detection can be perfectly achieved in perfect systems. An interaction with a lifetime longer than τ_C is, at least, one order of magnitude more probable for the invader than for a self presenter. These results are independent of the value of τ_C, while the magnitude of the value of $\mathcal{R}$ depends on the lifetime in which the analysis is made. Short lifetimes have small associated ratios and big lifetimes have higher ratios.

These results agree with the results obtained for circular frustrated systems. Perfect systems seem to be the solution for the algorithm of a computational system

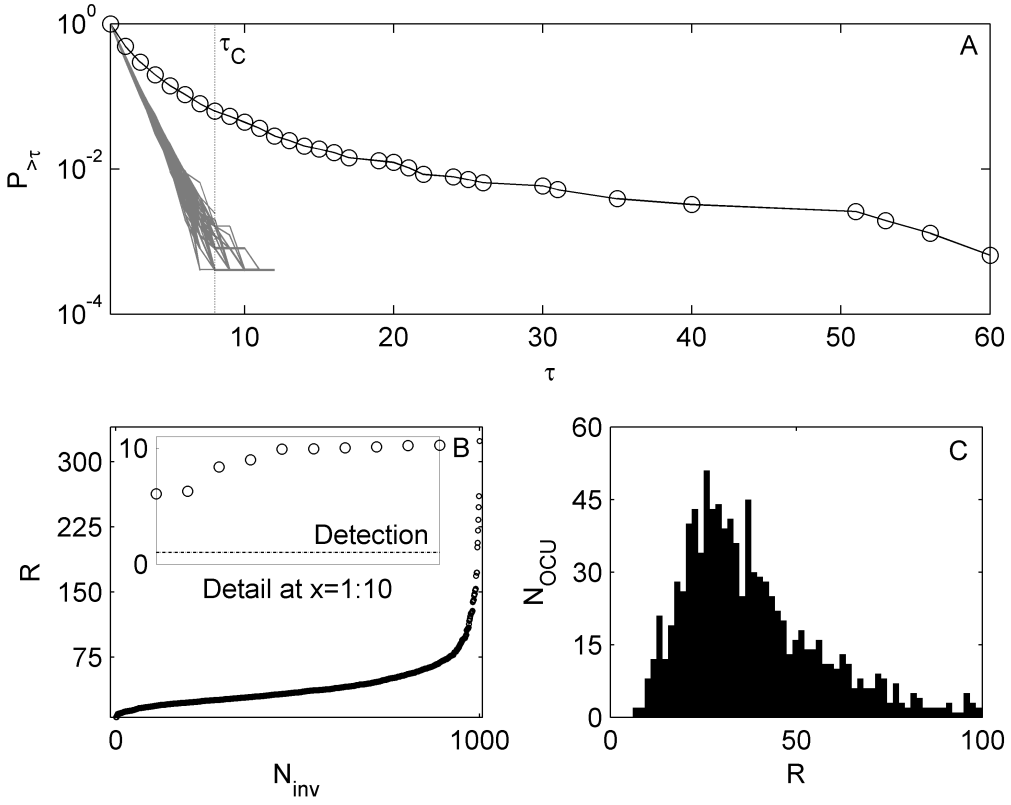


Figure 4.3: Numerical results obtained with an ideal system with 100 agents of each type. (A) Frequency of contacts lasting longer than τ iterations, for the agent presenting the foreign ligand (circles) and for the other presenter agents (grey lines), for W_{DET}=5000 iterations. (B) Detection ratio $\mathcal{R}$ calculated at τ_C=8 for all foreign ligands and (C) respective histogram.

which has a detection system as main goal. They do not seem a starting but an ending point for the computational system. However, perfect systems are not so general as required. One of the limitations of perfect systems is that all the ligands should be known in order to be introduced in the strict order of the ILists. Every new agent should be seen as a foreign agent, which means that every new self agent should be introduced in the system after the ILists are built. In addition, the increase in the system size requires the ILists to be modeled as a mathematical function so that the algorithm has practical applications. The codification of the ILists in mathematical functions is possible. However, the strict ordering of all the ligands as in the IList is not possible in a simple way. Thus, it is necessary to develop different approaches in CFSs so that the role of the structure of the ILists is not so crucial to accomplish detection.

The results of perfect systems were the beginning of an anomaly detection system that combines not only the intrusion detection capacity, but also the detection of anomalies related with homeostatic perturbations, the growth in the expression of some ligands instead of other and the abnormal combination of ligands in a given presentation shown by presenters.

4.1.2.2 Educated Systems

Emergent Repertoire of Educated Detectors

The main goal of the education process is to select a set of detectors that maximize frustration. About the real immune system is known that lymphocytes that strongly react with self presenters are eliminated and replaced by other detectors with different receptors. In the cellular frustration framework, the strength of a reaction is measured not by the affinity between ligands and receptors, - as in the traditional approaches -, but by the duration of the interaction. Thus, detectors that interact with maximal affinity can stay in the system if the interactions that it establishes have short lifetimes. In this algorithm, detectors are eliminated when they establish the longest interactions, independently of the affinity of the interaction.

In this method, every time a detector establishes an interaction longer than a τ_{neg} value, its IList is randomly reshuffled, as if a new detector was introduced in the system. Through a non-directional method of selection, all detectors that are not frustrated are eliminated. Ideally, this process should be ended when all detectors have ILists that allow the system to perform a maximally frustrated dynamics with conjugation lifetimes similar to the ones registered in perfect systems. Nonetheless, computationally this state is only possible with the ordered ILists. Different criteria can be defined to finish the selection of the detectors. Inspired by the real immune system, the population of detectors is educated when around 97% of the detectors are deleted, which corresponds to a τ_{neg}=75. This process is accomplished after around 40000 iterations, which means that the education process is not exhaustive. The education process reduces dramatically the conjugation lifetimes established by agents with a random and an educated population (Figure 4.4A and B, respectively). Each grey line represents the frequency of the interactions lasting longer than τ iterations ($P_{>\tau}$) in both systems, random and educated.

To understand the effect of the education process on the ILists, all the detectors'

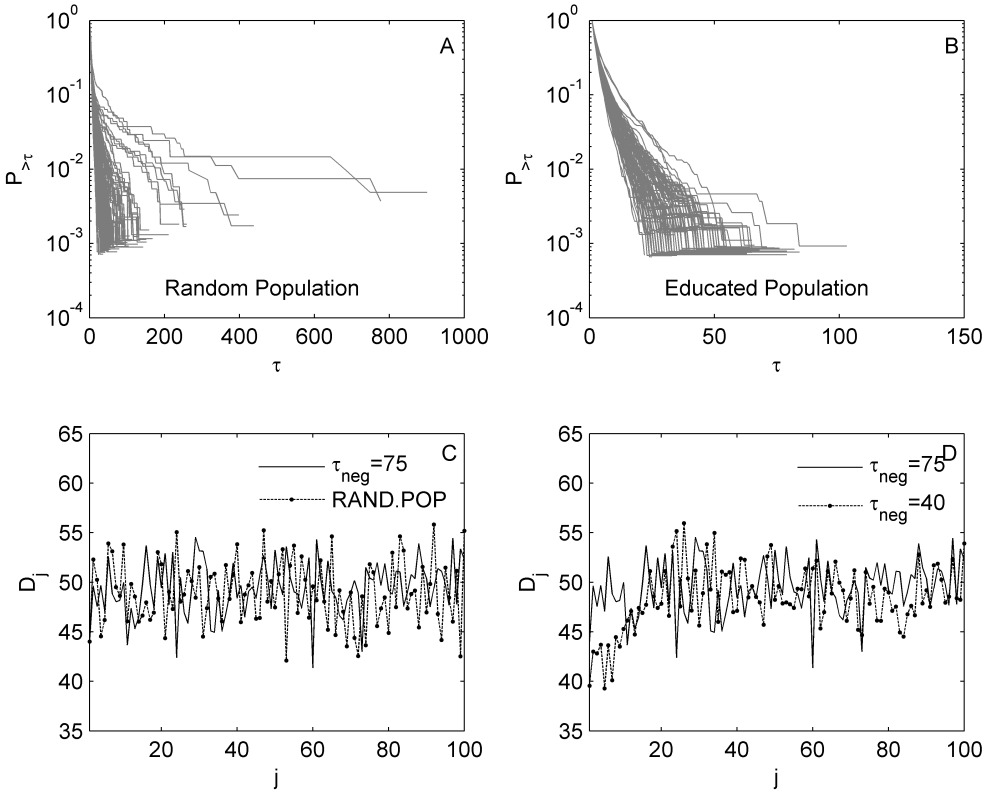


Figure 4.4: (A, B) Frequency of pairs lasting longer than τ iteration steps for every self-presenting agents(grey lines) and the average for all agents(black line), for a random and an educated population (τ_{ed}=75), respectively. (C, D) Average deviation of the value in a given position of the ILists for all detectors in an educated system and a random system, or between two educated systems with different levels of education, respectively.

ILists were analyzed and compared with the detectors' ILists in the perfect system. For each position of the ILists, the deviation between the ligand placed in the end of the education process and the ligand that would be there in the perfect system was calculated, D_j:

$$D_j = \frac{1}{N}\sum_{i=1}^{N}[L_i(j) - L_i^{perf}(j)] \tag{4.1}$$

where $[j] = j\theta(j)+(j+N)\theta(-j)$ represents the deviation from the ideal position. Here $\theta(j)$ is the Heaviside function. For instance, if in the first position of an IList there is a ligand that should be on the bottom, then this adds a N-1 contribution to the distance. The random and the educated systems have almost the same deviation in the ILists when compared to the perfect system (Figure 4.4C). A better

ordering is achieved if an extensive education process is applied which increases the number of deleted detectors (Figure 4.4D). Although random and educated systems have similar deviations, there is a dramatic effect on the frustrated dynamics generated. While a reduction of almost one order of magnitude in conjugation lifetimes is achieved with the education process, the typical interaction lifetimes are much greater than in the perfect case. This means that the system is far from the maximally frustrated dynamics generated in perfect systems.

Intrusion Detection in Educated Systems

With educated populations, results of self/nonself discrimination are far from perfect. Simulations were run introducing the same number of invaders, 1000 as in the perfect case. The no-detection rate was around 76%. This rate is improved with extensive education processes, but it never reaches 0%. After extensive education processes, the no-detection rate is around 15%.

The solution for perfect self/nonself discrimination is to assume that in educated systems intrusion detection is achieved not by a single population but by a set of educated populations. Inspired by the real immune system, several populations were educated with the same τ_{neg} (τ_{neg}=75). Several independent populations of detection ensure detection in educated systems, according with the sequence presented in Figure 4.2.

The invader has a ligand that is different from self, because it had never been presented in the education process. While detectors' ILists were shaped to avoid placing the ligands of the agents that have maximal affinity for them in top positions, the ligand of the invaders is randomly placed in the ILists. The sequence used increases the probability of the invader being detected. The increase in the number of detectors that ensure detection increases the probability of the detectors for which the invader has maximally affinity placing the ligand of the invader in the top position of the ILists. The question here is how many populations are required to ensure that a perfect discrimination is accomplished.

As in the previous section, 1000 invaders were introduced in the system and the dynamics generated was analyzed. Typical cumulative distributions for conjugation lifetimes that last longer than τ iterations are presented for a single population, in a no-detection and a detection case, in Figure 4.5 A and B, respectively. As in the perfect case, each grey line represents the dynamics of each presenter, while

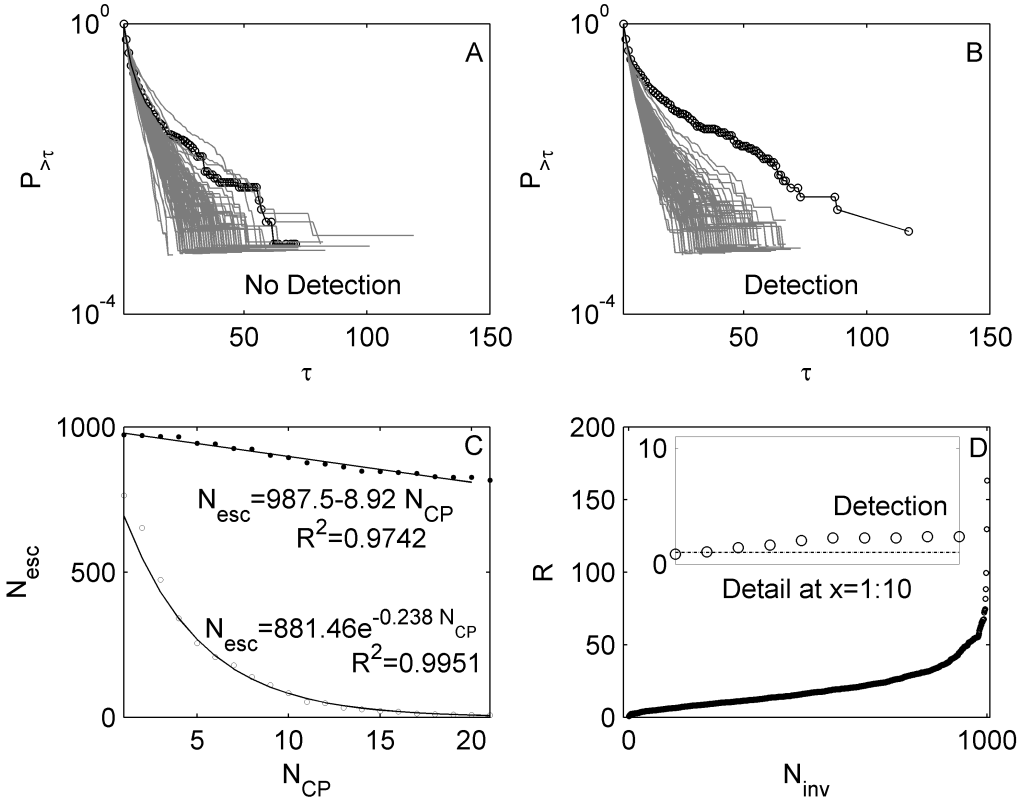


Figure 4.5: Typical cumulative distributions of interaction lifetimes for (A) no-detection and (B) detection cases. Cumulative distribution for conjugation lifetimes are presented in thin grey lines for self-presenters and with circles for the foreign ligand presenter. (C) Number of invaders escaping detection as a function of the number of consecutive detector populations used for educated (circles) or non-educated (dots). (D) Maximum detection ratios obtained after the sequence of detections, for each foreign ligand introduced.

the black line marked with circles represents the dynamics performed by the presenter that displays the foreign ligand. In Figure 4.5 B, the line that represents the foreign element clearly stands out from the remaining ones which represent the self presenters. It is interesting to notice, that both distributions have a dynamics similar to the one performed by self presenters and illustrated by the grey lines in the histograms. This last observation suggests that the education process generates an equivalent set of detectors, independently of the process in which the detectors are educated. The repertoire selection process is robust.

The number of invaders that escape detection decreases exponentially with the increase of the number of consecutive populations - N_{CP} - that scan the presentation. After 30 populations, only one invader can escape detection, all the other

999 invaders were detected at least by one population. If the same invaders are introduced in a set of no-educated populations, the number of invaders that escape detection linearly decreases at a slow rate with the number of consecutive random populations (Figure 4.5C). The ratios obtained for each invader are presented in Figure 4.5D. Only around 0.5% of the invaders have ratios below 2, whereas 75% of the invaders have ratios higher than 10, which means that the probability of an invader performing longer conjugations is 10 times higher for the invader than the less frustrated self presenter. These differences could be greatly increased if the triggering event was based on the frequency of formation of long conjugations. For instance, if it required a consecutive number of events with a given lifetime to trigger a response.

The detection ratios are smaller if compared with the ratios obtained for perfect systems. This was antecipated because in educated systems the dynamics generated by the educated ILists is not maximally frustrated. When the invader is introduced in the system, its ligand appears in a random position of the ILists of all detectors. Nevertheless, the relative order of the remaining ligands is not perfect either. Consequently other self ligands perform conjugations that are longer than in the perfect case. Thus, the ratios decrease.

An extensive education process or an increase in the number of populations considered will be enough to obtain perfect self/nonself discrimination. However, the main goal of this section is to show how the main ideas started and evolved from this first approach. In the next sections better model concerns the intrusion detection and homeostatic responses to perturbations will be discussed in the light of the CF framework.

4.2 Positive Education

In immunology, it is known that the positive education process ensures that T cells that can not interact with APCs are not positively selected and die by neglect [1, 2, 17].

The positive education was the most puzzling concept in the CF framework. Several disconnected results were obtained in different phases of this work, concerning the goal of this selection process. In symmetric systems with total connectivity, the positive education process seemed not to play any effect. On the other side, the positive education process adjusts the number of subpopulations in asymmetric systems and it increases the interactivity between presenters and detectors, although the interaction lifetimes registered in the dynamics were the same in most cases, with or without the process. However, in systems with limited connectivity, it became clear that the positive education can be responsible for the decrease of the threshold τ_{neg} during the education process.

The discussion of the effect of the positive education will be held with different systems throughout this section . These systems will never be used again in this work. However, they were built to clearly highlight the effect of the positive education on each case. Due to this fact, a small section of Simulations and Parameters will be presented only with the parameters that are common to all the systems considered. The details of each system will be presented in the Numerical Results section together with the results obtained in each case.

4.2.1 Simulations and Parameters

During the positive education process, all the detectors that do not bind for τ_{pos} iterations are eliminated and new incoming detectors are introduced in the system. These new detectors have reshuffled ILists as well as a random ligand.

In the beginning of the positive education process, τ_{pos} is initiated with the value 5000, the value of the number of iterations W_{EDU} taken between its update. τ_{pos} is updated to the maximal value that a detector remains without establishing an interaction with a presenter. After this, every time a detector remains τ_{pos} iterations without interacting, it is eliminated and another detector enters the system. If none of the detectors interacts during W_{EDU} time steps, the value of τ_{pos} is again updated and the process goes on.

4.2.2 Numerical Results

4.2.2.1 Positive Education regulates detectors subpopulations

To understand the effect of positive education on the regulation in number of the subpopulations, a 2-cluster asymmetric system is considered. Presenters were differently distributed: 60 and 40 presenters are placed in clusters 1 and 2, respectively. All the detectors are placed initially in cluster 1 (Figure 4.6).

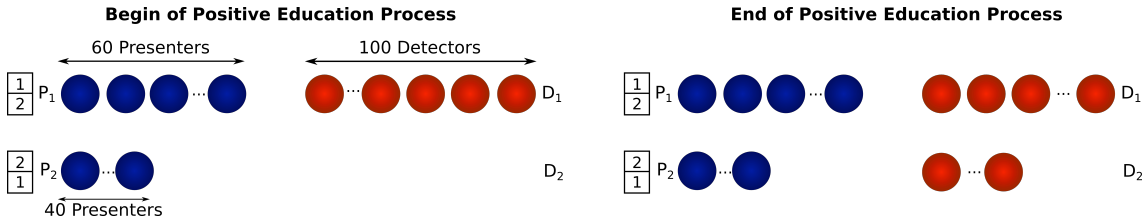


Figure 4.6: Assymetric system considered in the beginning and in the end of the positive education process.

The evolution of the number of detectors in each cluster is presented with the duration of the simulation (Figure 4.7). The total number of detectors in cluster 1 - N_{D_1} - tends to be equal to the number of presenters in the same cluster - N_{P_1} - and the same for cluster 2, that is, the number of detectors and presenters in the second cluster is almost the same - $N_{D_1} \approx N_{P_1}$ and $N_{D_2} \approx N_{P_2}$, as presented in Figure 4.7 .

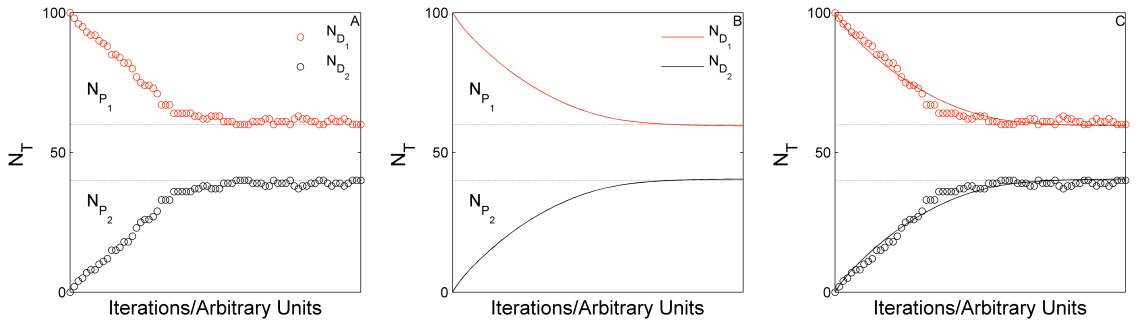


Figure 4.7: Evolution of the number of detectors in each cluster along the positive education process: (A) cellular automaton model; (B) mean field equations approach and (C) both cases.

To validate this result, mean field equations were derived for all the conjugated and non-conjugated agents. Also as in the previous sections, the interactions that contribute to the formation and to the destruction of each species were considered. Whereas in the other case detectors have educated ILists (Section 3.1.2). Thus,

different probabilities are considered according to the ligands of the presenters with which the detector is interacting. In order to simplify the equations, only three probabilities of optimizations were considered: p_M, p_I and p_S - with p_M=0.5, p_I=0.3 and p_S=0.7 as in section 3.1.2. Here, an additional term that models the change of cluster of detectors during the education process is introduced in the equations:

$$\frac{dn_{P_1D_1}}{dt} = n_{D_1\phi}(n_{P_1\phi} + n_{P_1D_2}) + p_I n_{P_1\phi} n_{P_2D_1} + n_{P_1D_2}(p_M n_{P_1D_1} + p_I n_{P_2D_1}) - n_{P_1D_1}(p_{diss} + p_S n_{P_{2\phi}} + p_M n_{P_1D_2})$$

$$\frac{dn_{P_1D_2}}{dt} = n_{P_1} n_{D_2} + n_{P_1}(p_M n_{P_1D_2} + p_S n_{P_2D_2}) - n_{P_1D_2}(p_{diss} + n_{D_{1\phi}} + p_M n_{P_1D_1} + 2p_I n_{P_2D_1} + p_M n_{P_{1\phi}} + p_I n_{P_{2\phi}})$$

$$\frac{dn_{P_1\phi}}{dt} = p_{diss}(n_{P_1D_1} + n_{P_1D_2}) + n_{P_1D_1}(p_M n_{P_1\phi} + p_S n_{P_2\phi} + p_M n_{P_1D_2}) + n_{P_1D_2} (p_M n_{P_1\phi} + p_I n_{P_2\phi} + p_I n_{P_2D_1}) - n_{P_1\phi}(n_{D_{1\phi}} + n_{D_{2\phi}} + p_M n_{P_1D_1} + p_I n_{P_2D_1} + p_M n_{P_1D_2} + p_S n_{P_2D_2})$$

$$\frac{dn_{D_1\phi}}{dt} = p_{diss}(n_{P_1D_1} + n_{P_2D_1}) + n_{P_2D_1}(n_{D_2\phi} + p_I n_{P_1D_2} + p_M n_{P_2D_2}) - n_{D_1\phi}(n_{P_1\phi} + n_{P_2\phi} + n_{P_1D_2} - 0.5\beta_1 n_{D_1\phi} + 0.5\beta_2 n_{D_2\phi})$$

Here $0.5\beta_1 n_{D_1\phi}$ and $0.5\beta_2 n_{D_2\phi}$ represents the fraction of detectors that are eliminated and created due to the lack of interactions of $D_1\phi$ and $D_2\phi$ agents, respectively, and $\beta_{1/2} \propto (1\text{-}\tau_{B_{1/2\phi}})^{\tau_{pos}}\ n_{B_{1/2\phi}}$ models the triggering of positive selection. A small probability of natural dissociation can be considered, p_{diss}=0.001. The other equations can be easily obtained by the replacement of (P_1, P_2, D_1, D_2)→(P_2, P_1, D_2, D_1).

More processes can be considered to account for the complex optimization process performed by each agent. This would introduce more parameters. However, the increase in the complexity would not be translated into a deeper comprehension

of the positive selection process, which is captured with these simple assumptions.

The same system which was simulated with cellular automaton. There is a good agreement between the results obtained in the cellular automata model and the results obtained through the dynamical mean field-like equations(Figure 4.7C). Despite the fluctuations, the positive education process leads the system to a configuration in which the number of detectors is equal to the number of presenters in the same cluster, $N_{D_1} \approx N_{P_1} = 60$ and $N_{D_2} \approx N_{P_2} = 40$, in the end of the positive education (Figure 4.6B).

The final configuration after the education process is the one that ensures that detectors have presenters that will always accept them as preferred agents (Figure 4.8A). This prevents detectors from not being positively selected. Here, in the configuration obtained all the numerous presenters P_1 will accept detectors D_1 if they are alone or with a detector from the other subtype, D_2. This mechanism ensures that detectors interact with these presenters and they avoid elimination due to lack of interactions.

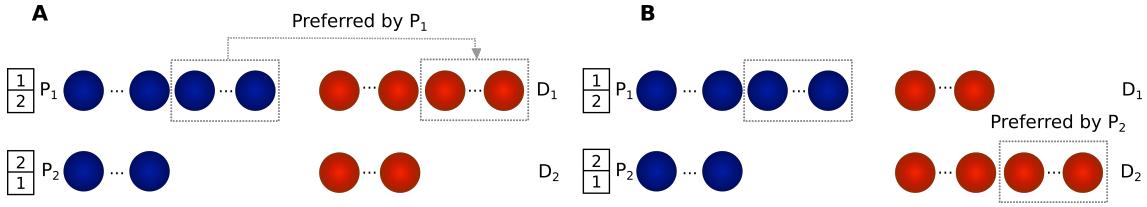


Figure 4.8: (A) Configuration of the system after the selection process. (B) Alternative asymmetric configuration.

The opposite configuration $N_{D_1} = N_{P_2}$ and $N_{D_2} = N_{P_1}$ promotes that D_2 will have difficulties in interacting with P_1 because they prefer D_1 (Figure 4.8B). Consequently, D_2 will only be able to interact with P_1 that are alone, because the non-conjugated P_1 are the ones that will accept D_1. None of the conjugated D_1 will change conjugation because they are satisfied with D_1 and even if they are conjugated with other D_2, they will not change. Interactions with P_2 are also difficult because they are in small number in comparison with D_2 and the competition for these presenters is high. In this configuration the detectors of D_2 subtype have difficulty in interacting with presenters and they can not easily avoid elimination.

It is easy to understand that the positive education balances the number of presenters and detectors in systems with different numbers of agents within the clusters. However, does this mechanism have any relevance in symmetrical systems for which presenter agents in different subtypes appear in equal numbers? In order

to better understand the relevance of the positive education process in symmetric systems, three different education conditions were imposed to a 2-cluster system with 50 agents per cluster. In the first simulation only the positive education was considered (Figure 4.9A), while in the second it is assumed that detectors that exceed the τ_{neg} of conjugation are replaced and the new detectors are placed in an arbitrary cluster - negative education process with change of ligands (Figure 4.9B). Finally, in the last simulation both processes were considered (Figure 4.9C).

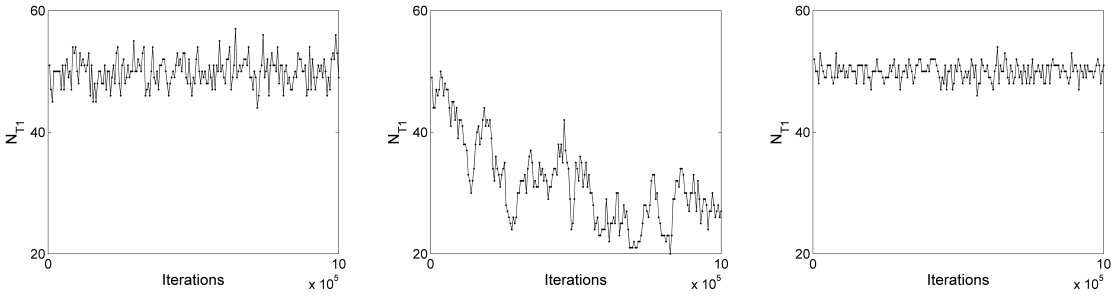


Figure 4.9: Number of detectors in the first cluster along the education process, considering positive education, negative and both processes, A, B and C, respectively.

In systems in which only one process was considered, positive or negative education, the number of agents in each cluster fluctuates much more than when both precesses were considered. The positive education process ensures that during the education process the number of detectors in each cluster is almost the same.

The positive education process is the mechanism responsible for the regulation of the number of detectors in each cluster during the education process. Bearing this in mind, symmetric systems will be considered from now on to discuss the remaining goals of the positive education process.

4.2.2.2 Positive Education adjusts the Network of Interactions

The previous results show that positive education plays a role in the regulation of the number of detectors in each subtype. This mechanism is responsible for ensuring that although different detectors are continuously entering the system, the number of detectors in each subtype is almost the same as the number of presenters in the corresponding subtype. Here, the effect of the positive selection on the reduction of the conjugation lifetimes will be studied. From the previous section, nothing suggests that positive education process could favor the convergence of the system. However, a deeper comprehension of the mechanisms in the detectors' selection pro-

cess imposes a detailed study. To emphasize the importance of positive education, a system in which a ligand is presented by several presenters was selected. In addition, restricted connectivities were considered. The system selected plus the reduced connectivity will favor the selection of ligands in the top positions of ILists will be crucial for the selection or not of each detector. The ILists should ensure that each detector interacts with presenters and should also ensure that this interaction is frustrated. Any small mistake in the ILists concerning one of these two aspects will dictate the elimination of the detector.

A system with N_P=N_D=60 and 2 clusters with the same number of agents was considered (Figure 4.10). Agents are represented by circles, together with their ligand - a number between 1 and 26 for the presenters and equal to 1 or 2 for the detectors. The system has groups of agents sharing a common ligand (for example, 21 and 22 in the first cluster are presented by 5 presenters each). Presenters have two types of receptors, all presenters of the first cluster have detectors of the first cluster on the top of their IList, followed by the ones of the second cluster. In the second cluster, presenters do the opposite.

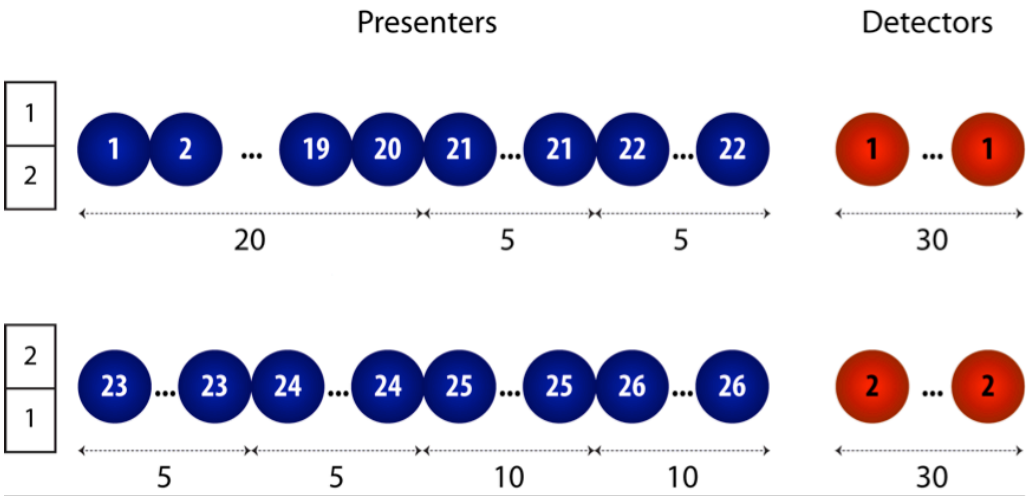


Figure 4.10: Population considered in the text, with repeated ligands displayed by presenter agents.

To study the convergence of the education process with or without positive education, this system was simulated with 3 different connectivities. One in which each detector interacts with all the presenters in the system, i.e. k=26. Another in which each detector interacts with the top 20 ligands, k=20, and finally, a third one which has even smaller connectivity, k=10. The generic decay of the τ_{neg} during the education process is presented in the case only negative selection is considered, NS,

and in the case both processes were simulated - PS+NS. Ten independent decays with different connectivities for the detectors were simulated in each case during 10^7 iterations each.

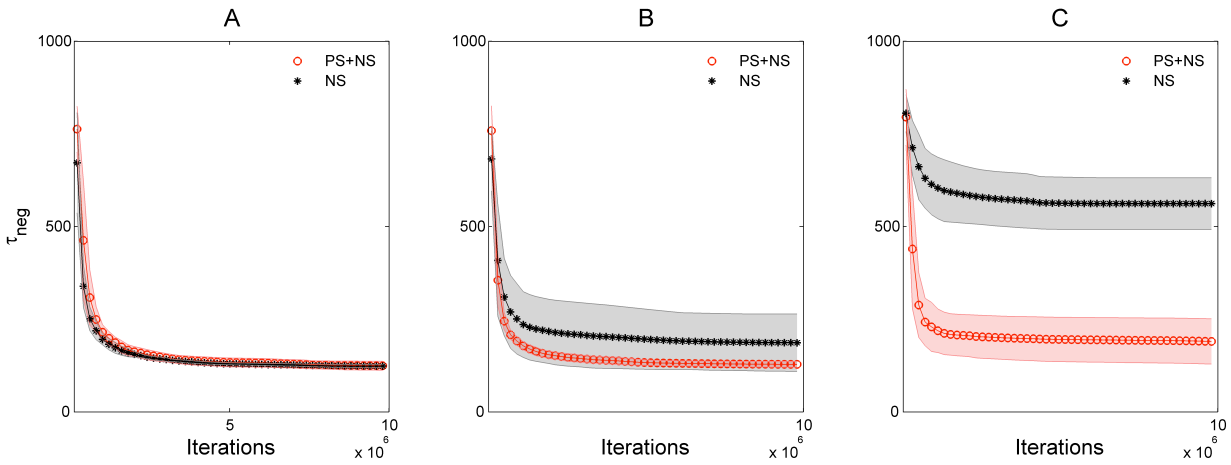


Figure 4.11: Decay of τ_{neg} for systems with and without positive education, NS+NP and NS, and different connectivities: (A) k=26, (B) k=20 and (C) k=10.

In systems with total connectivity, the decay of the conjugation lifetime - τ_{neg} - is similar, with or without positive education (Figure 4.11A). A different result is obtained if the connectivity of the detectors is restricted. For smaller connectivities, positive selection is crucial for decreasing τ_{neg}, as shown in Figure 4.11B and C. The smaller the connectivity, the higher the difference between the final τ_{neg}, with and without positive selection.

To analyze the effect of the different education processes on the dynamics generated, cumulative histograms are presented for systems with different connectivities, k=26 and k=10 (Figure 4.12 and Figure 4.13, respectively). The red lines represent agents from the first cluster, while the black lines represent agents from the second.

The number and the duration of the interactions established are almost the same with only negative education or with both processes for systems with total connectivity (Figure 4.12A and B). There is a difference in the probability of each detector staying in a non-conjugated state. In systems with only negative education, agents from the first cluster have higher probability of staying alone (Figure 4.12C). In systems with positive and negative education the probability is equal for all the detectors (Figure 4.12D).

For systems with limited connectivity the results are completely different. Due to the absence of the positive selection, detectors were not able to select the net-

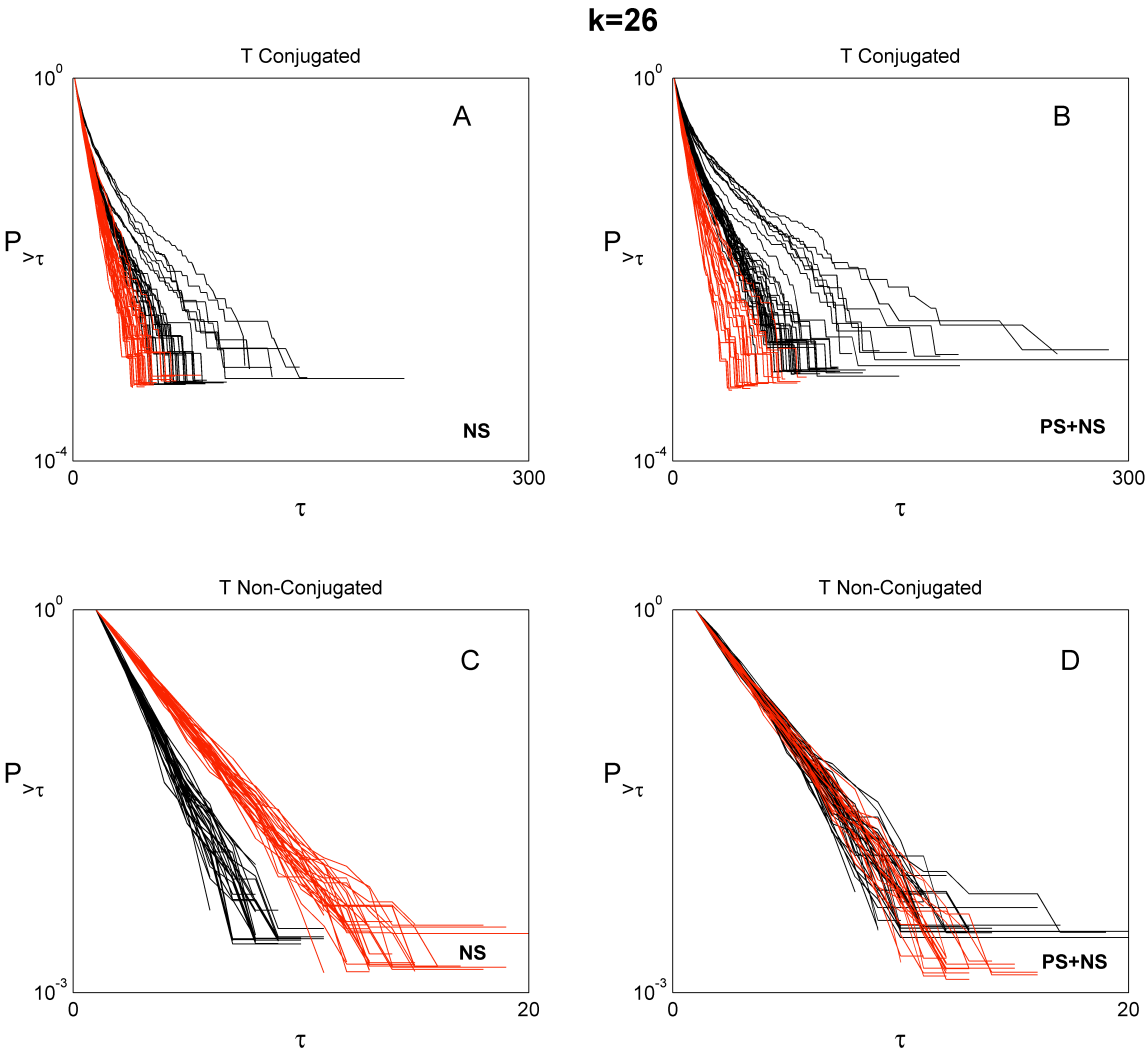


Figure 4.12: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$ for each detector (A, B) or the probability that detector stays non-conjugated for a time longer that τ iterations (C, D) for a system with k=26. Different education processes are considered: only negative selection, NS (left), or positive and negative selection processes, PS+NS (right). Red lines represent agents from the first cluster, while black lines represent agents from the second.

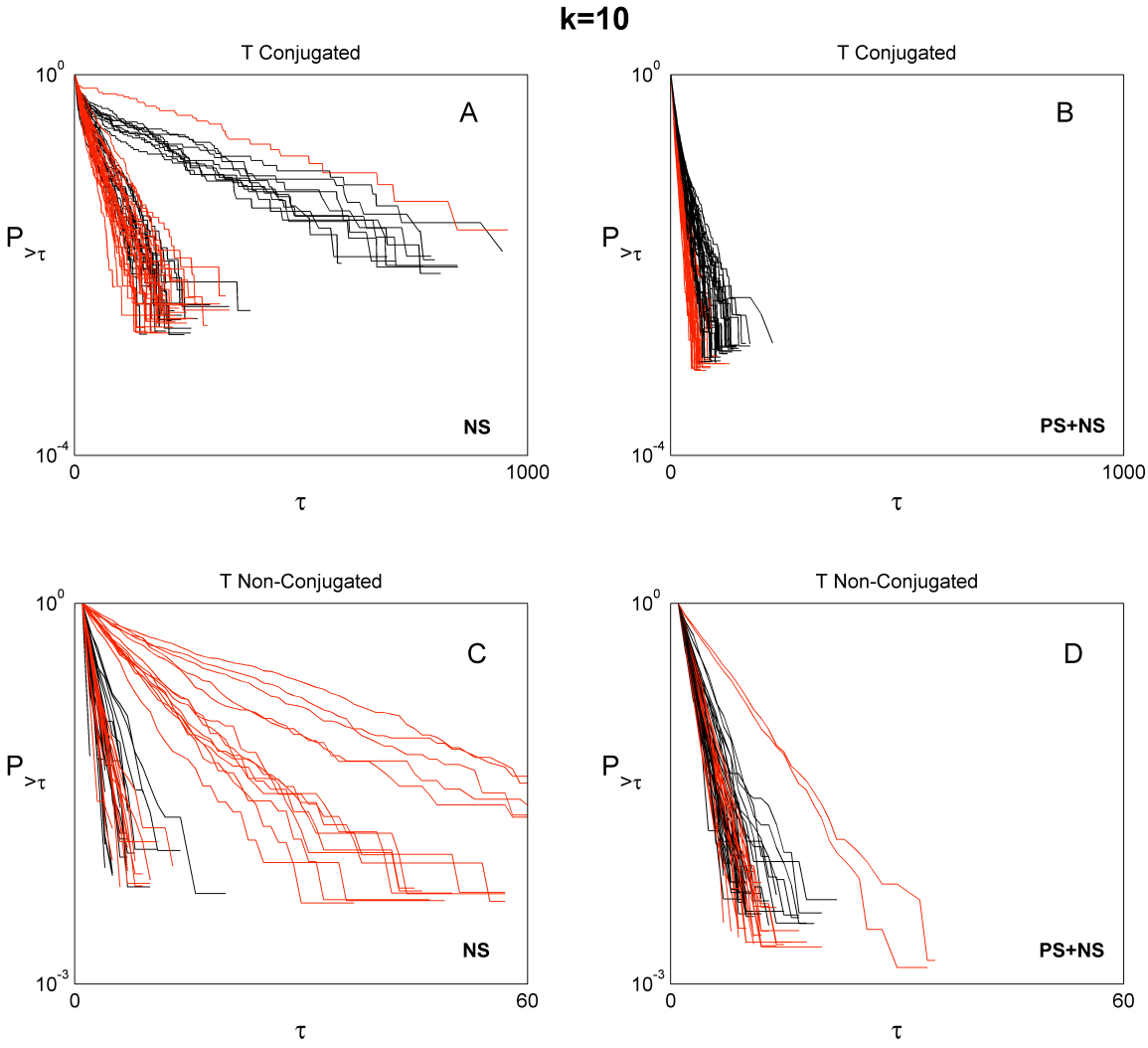


Figure 4.13: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$ for each detector (A, B) or the probability that detector stays non-conjugated for a time longer that τ iterations (C, D) for a system with k=10. Different education processes are considered: only negative selection, NS (left), or positive and negative selection processes, PS+NS (right). Red lines represent agents from the first cluster, while black lines represent agents from the second.

work that allows the minimization of τ_{neg}. Hence, longer conjugation lifetimes are performed more frequently for the negatively educated system (Figure 4.13 A and B). Furthermore, no-conjugation lifetimes are also more probable in this system (Figure 4.13 C and D).

The smallest decrease of the τ_{neg} during the education process in the absence of the positive education can be easily understood with a toy model with small diversity and restricted connectivity. A 2-cluster system with only 3 different ligands presented by presenters is considered. If each detector is allowed to interact only with 2 of the 3 possible ligands, 12 different ILists are available (Figure 4.14). In black are represented the ILists that ensure a maximally frustrated dynamics in the system. The ILists that should be eliminated by negative education are shown in red, while the ILists that should be eliminated by positive education because the detectors do not establish interactions properly are represented in blue.

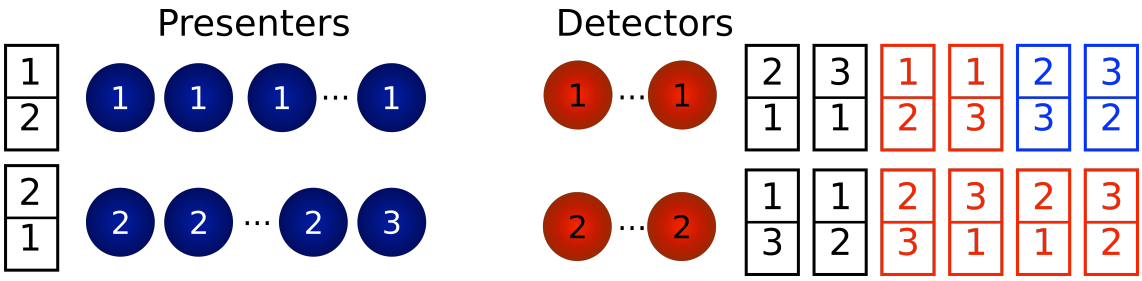


Figure 4.14: Representation of a simple model that highlights the importance of positive selection in systems with limited connectivity. Presenters of the first subtype present ligand 1, while presenters of subtype II present either ligand 2 or 3. Detectors with ILists represented in red establish stable pairs and consequently are eliminated by negative selection. Detectors represented in black form a frustrated set: and conjugation involving these agents can always be destroyed either by a presenter or a detector. Similarly detectors with ILists represented in blue do not establish long contacts with presenters 2 or 3, because any detector of subtype II destabilizes the pair.

In the absence of positive selection, the detectors in black are selected together with the ones in blue (Figure 4.15 a, b). Moreover, the number of detectors with the ILists in blue increases. Firstly, they are not eliminated by negative education, because they almost never interact. Secondly, they are continuously created, that is, for each eliminated detector by negative selection in cluster 1, a detector with the green ILists is generated with ≈17% of probability. As a consequence, the global frustration of the system decreases and the τ_{neg} in the end of the education process is higher than the final τ_{neg} achieved in a selection process with positive and negative

selection (Figure 4.15 c, d).

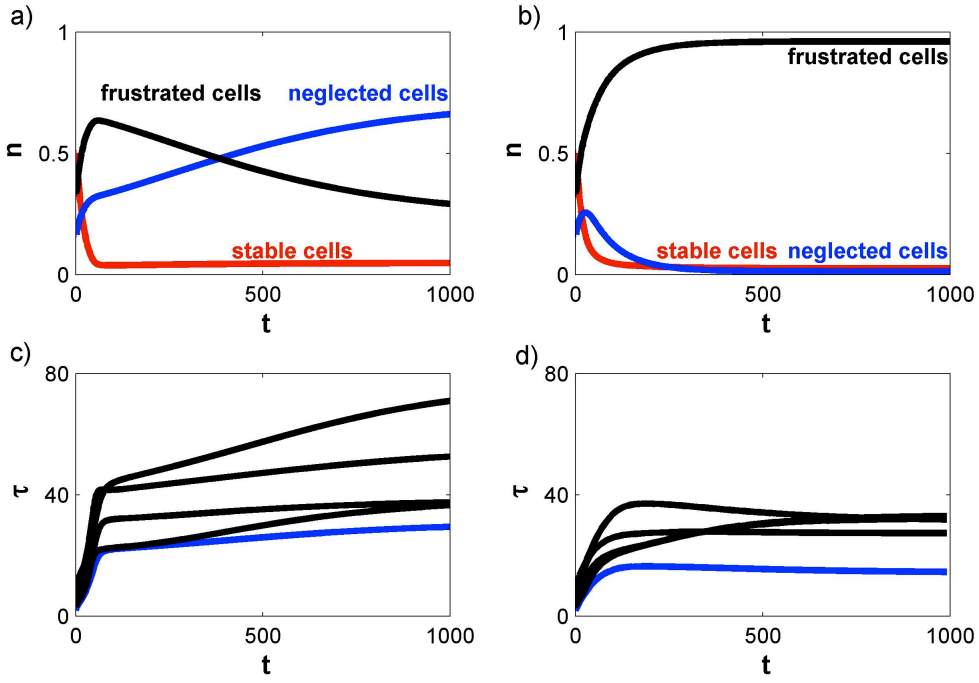


Figure 4.15: Impact of positive and negative selection on the evolution of detectors frequencies for the simplified model in Figure 4.14. In a) and c) only negative selection is applied. In b) and d) positive and negative selection are applied simultaneously. Lines in blue in a) and b) represent the total number of detectors with ILists represented in blue in Figure 4.14; in red are represented the total number of detectors that establish stable conjugations; in black are represented the total number of detectors engaging in frustrated interactions. In c) and d) are displayed conjugation lifetimes for the most relevant conjugates in the population. As stable agents are eliminated, their lifetimes are not represented.

These results show that if no positive selection is applied, neglected detectors accumulate, and the maximum conjugation lifetimes are larger than in the model in which positive selection is applied and these detectors are eliminated. These results agree with numerical results obtained for cellular automata with more ligands.

4.3 Negative Education

In Immunology, the negative selection process eliminates all T cells which have highest affinities to self peptides presented in the Thymus [1, 2]. This elimination ensures that T cells do not react in a harmful way with self cells in the periphery. The main mission of the negative education process is to reduce the maximal affinity with which the MHC complex is recognized by detectors.

In CFSs the goal of the negative education is not to reduce the affinity of the interactions between agents, but to increase the frustration of the dynamics that is generated between presenters and detectors. This process should warranty that detectors cooperate in the detection task, regardless of which detectors perform the detection.

The selection of detectors by the education process is absolutely crucial in CFSs. Without a frustrated dynamics the system can not perform any of the detection tasks proposed. Due to this, several studies about the process were carried out, concerning the convergence of the education process and the effect of the education process on the ILists and on the dynamics of the system. All the knowledge about this process will be presented along the next section.

4.3.1 Simulations and Parameters

Contrary to the previous section, in which different systems were used, in this section the same generic system is considered: a symmetric system with 60 agents of each type, equally divided into clusters - 2 or 3 clusters. The connectivity is total, all agents interact without restrictions with the agents of the opposite type. Presenters have different ligands within the cluster but the same receptor, which is built in such a way that:

$$R_C(i) = (C+(i-1))\theta(N_c-(C+(i-1)))+(C+(i-1)-N_c)\theta((C+(i-1)-N_c)) \quad (4.2)$$

in which i represents the position in the receptor, C the cluster, N_C the number of clusters and θ represents a discrete form of the Heaviside step function as presented in section 3.1.1.1. Detectors have the same ligand within the same cluster but random receptors at the beginning of the education process.

All systems were simulated during $\approx 10^7$ iterations or until τ_{neg} of the education process reached a predefined τ_{ed} value. This fixed value of τ_{ed} is the minimal value

τ_{neg} achieved the first educated population after 10^7 iterations. While the fixed number of iterations is used to study the convergence of the education process, the fixed τ_{ed} value is used to educate the extended repertoire of detectors - this criterion ensures that all populations are almost at the same education stage. Regardless of the stopping criterion selected, τ_{neg} is equal to 5000 at the beginning of the process and it is updated if, none of the detectors remains conjugated during τ_{neg} iterations, during the education window (W_{EDU}=5000). In this case, τ_{neg} decreases to the maximal conjugation lifetime established in W_{EDU} iterations. Every time that, during the education process, a detector remains conjugated τ_{neg} iterations with a presenter, the detector is eliminated and replaced by a new incoming detector with a random receptor.

To study the negative education process in different situations, several conditions were changed, such as the number of agents, the number of clusters, the connectivity, etc. The conditions that are changed in each case are properly presented before the presentation of the corresponding numerical results.

In order to increase the comprehension of the results, this section is divided in two parts. In the first, the convergence of the negative education process will be presented. Then, the effect of the negative education process on the ordering of the ILists and on the dynamics that is generated in an educated system will be shown.

4.3.2 Numerical Results

4.3.2.1 Increase in number of clusters allows better convergence

To estimate the effect of the introduction of different subtypes, simulations with the same number of agents - 60 agents per agent type -, but different number of subtypes were performed (Figure 4.16). The first system considered is a 2-cluster system. Presenters and detectors are equally divided into clusters (N_{P_1}=N_{D_1}=N_{P_2}=N_{D_2}=30). The numbers inscribed represent the ligand of each agent. Presenters have the same receptor inside the cluster which codes the same IList. In opposition, detectors have different receptors that code different ILists, which randomly rank all the ligands. The ILists of presenters are represented on the left, while the ILists of two arbitrary detectors are presented on the right .

The negative education process was performed five times with the same system but different random seeds, during 1x10^7iterations. For each simulation, the decay of τ_{neg} was registered. A linear interpolation was applied to all decays, and the

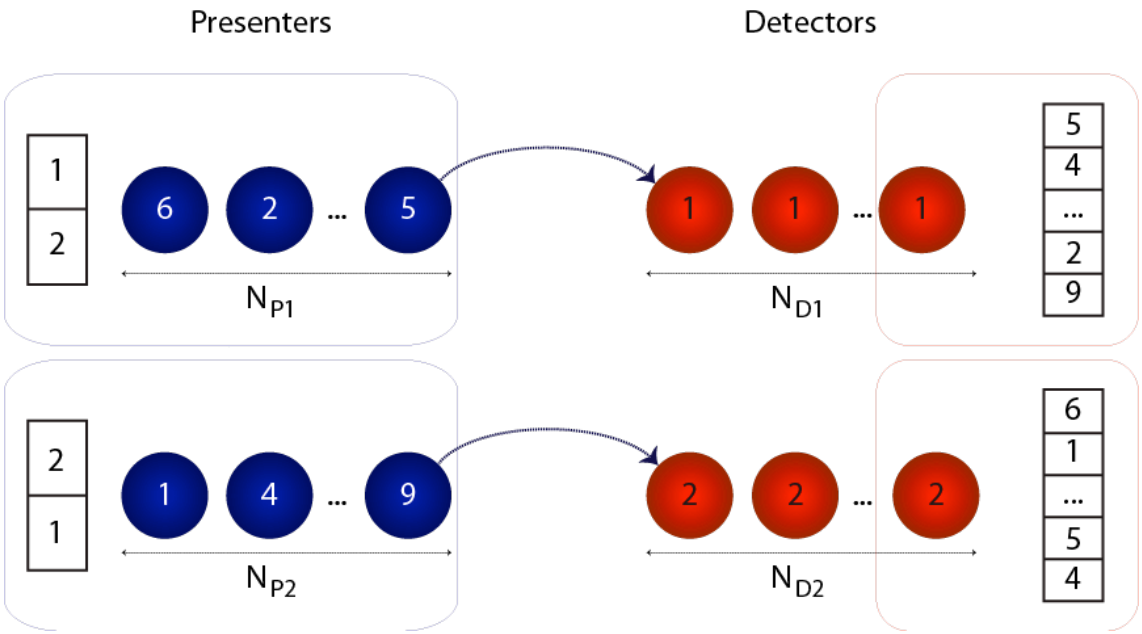


Figure 4.16: Generic system with 2 clusters or subpopulations.

average of all decays, as well as the error bars were calculated and presented in Figure 4.17. The τ_{neg} in a 2-cluster system decays to half of the initial value.

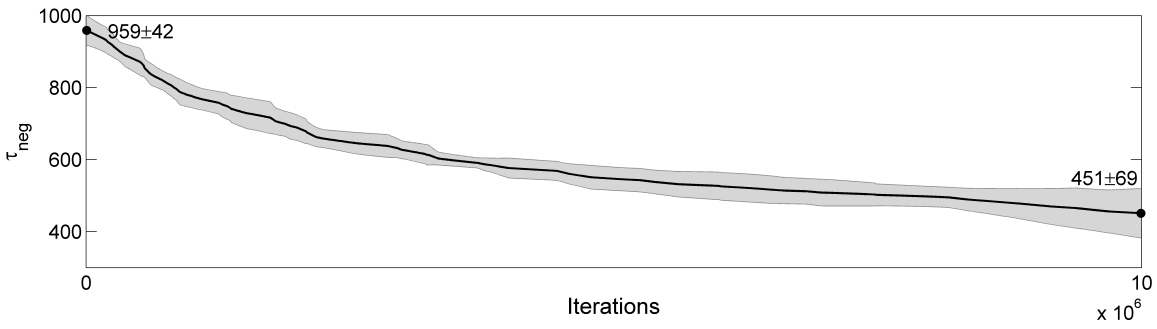


Figure 4.17: τ_{neg} decay for a system with two clusters. A linear interpolation was applied to five independent decays of τ_{neg}, and the average of all decays, as well as the error bars were determined.

To study the effect of the introduction of more clusters, the generic decay obtained in a 2-cluster system was compared with the decays obtained is systems with 3, 4, 6 and 10 clusters and the same number of agents. The simulation was repeated with the same number of agents equally distributed in different number of clusters. Five independent decays were collected for each system. The decay of τ_{neg}/τ_{neg_I} throughout the simulation is represented for all systems (Figure 4.18). Also, the average initial and final value are presented - τ_{neg_i} and τ_{neg_f}-, as well as the respective

error bars.

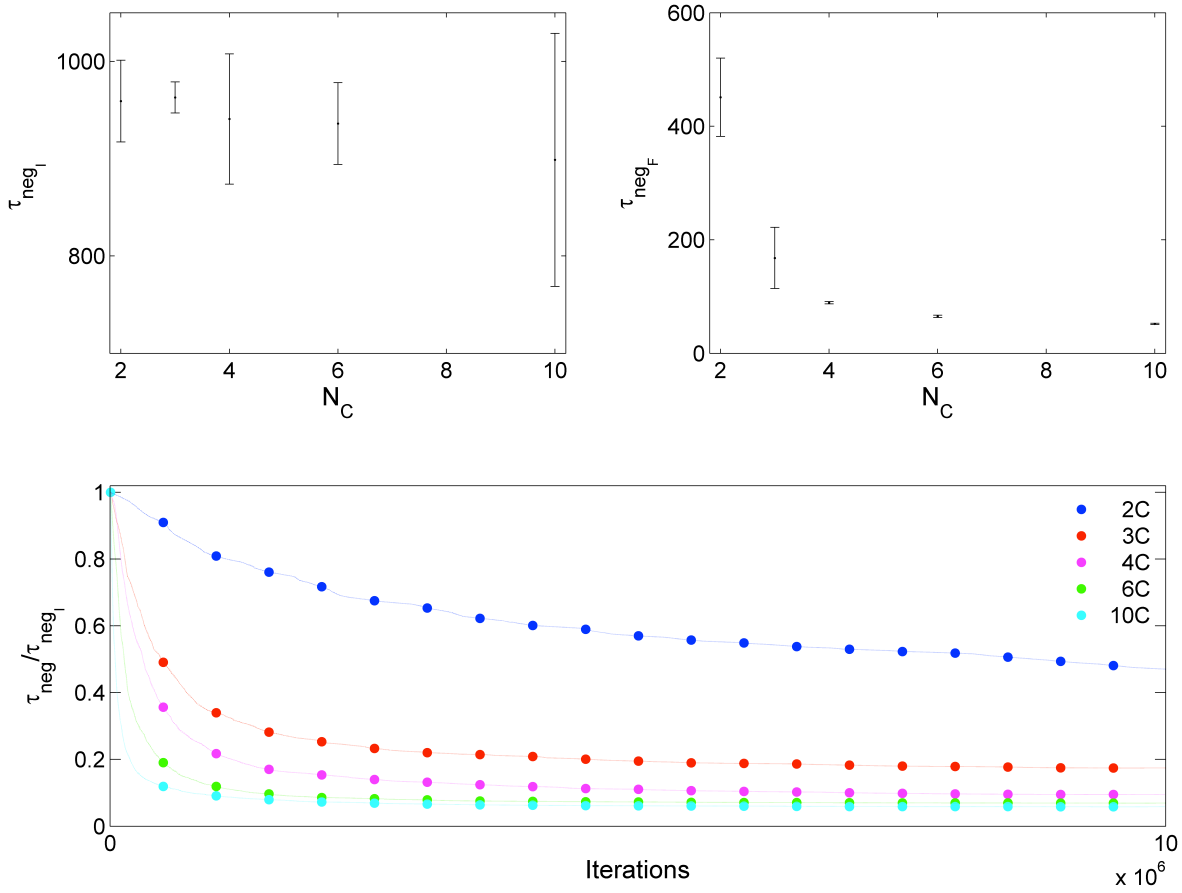


Figure 4.18: Top Left: Average initial threshold times of the negative education process, τ_{neg_I}, and respective standard deviations as a function of the number of clusters, N_C. Top Right: Final average threshold times of the negative education process, τ_{neg_F} and respective error bars, as a function of the number of clusters, N_C. Bottom: Decay of τ_{neg}/τ_{neg_I} throughout the simulation, for systems with 2, 3, 4, 6 and 10 clusters.

The initial value of the τ_{neg} is independent of the number of clusters and it is similar in all systems. In opposition, its final value depends on the number of clusters considered. The smallest τ_{neg} is obtained for the 10-cluster systems while the biggest τ_{neg} is registered for a 2-cluster system, 52±1 and 461±69, respectively. The results obtained indicate that the smaller the number of clusters, the smaller the decrease of τ_{neg} during the negative education process. It is also interesting to notice that the same generic curve is obtained for all the systems - a sharp decrease of τ_{neg} occurs in the beginning of the simulation, followed by a much slower decrease

in the end. The higher the number of clusters, the higher the sharp initial decrease is. Both the τ_{neg} and the standard deviation decrease with the introduction of subtypes. Table 4.1 summarizes the composition of the systems and the final value of the τ_{neg} obtained.

Table 4.1: Final τ_{neg} with the composition of the system

Clusters	Agents per cluster	τ_{neg}
2	30	451±69
3	30	168±54
4	15	89±2
6	10	56±2
10	6	52±1

The introduction of more clusters allows better education. Different time scales in the conjugation lifetimes are added with the increase of the number of clusters. This can be easily understood when 2 and 3-cluster systems are compared. If another cluster is added to the system, the total number of the agents is equally divided by the 3 clusters. While in a system with two clusters one half of the ligands should be avoided in the first half of the top positions for each detector, in the case of 3 clusters there are now only one third of ligands to avoid. The number of longer conjugations due to detectors that have maximal affinity for presenters which also prefer them will be also reduced with the additional clusters. Hence, a lower number of iterations is needed to select a population with the same value of τ_{ed}.

The results discussed here were obtained for small systems (N_P=N_D=60). Can these results be extended to bigger systems? Is the negative selection process scalable? The scalability of the negative education process will be discussed in the next section.

4.3.2.2 Convergence is more difficult in larger systems

In the previous section it was shown that the negative education process is possible and that it is favored by the increase in the number of clusters. However, only systems with 60 agents per type were considered. In this section the scalability of the negative education process will be discussed. Simulations were performed with a system with 3 clusters, due to easier convergence when compared with 2-cluster systems. Presenters display a different ligand per agent while detectors have ligands

equal to 1, 2 or 3 depending on the cluster. Presenters have the same receptor within the cluster. Detectors have arbitrary receptors that list all ligands in a random order. Symmetric systems with 90, 150, and 300 agents per type were considered. The respective education processes were analyzed and compared with that obtained for the 60-agents system presented in the last section. As in the previous section, the decay of the τ_{neg}/τ_{neg_I} is presented, for all the systems in Figure 4.19.

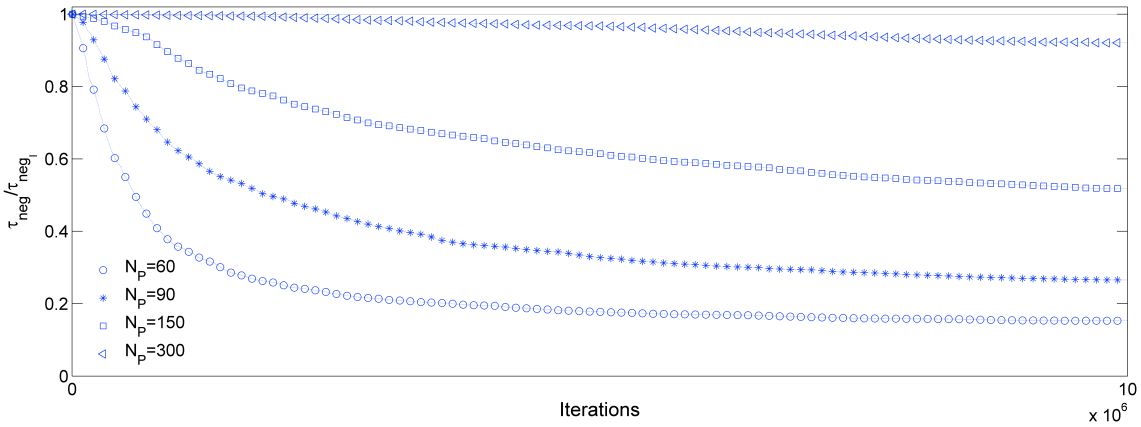


Figure 4.19: τ_{neg}/τ_{neg_I} decay for systems with 60, 90, 150 and 300 agents per type.

The final value of τ_{neg}/τ_{neg_I} is minimal for a system with 60 agents (0.150±0.10), followed by the systems with 90 (0.260±0.06), 150 (0.520±0.05), and finally for systems with 300 (0.92±0.04). In the latter case, the τ_{neg}/τ_{neg_I} is almost the same before and after the negative education process.

The reason why the complexity of the education process increases with the increase in the number of ligands is easy to understand. A linear increase in the number of ligands represents an exponential increase in the number of possible ILists. For example, an increase of thirty ligands, from 60 to 90 ligands, corresponds to an increase in the number of possible ILists from 60!≈8.3x10^{81} to 90!≈1.5x10^{138}. In a system with 300 ligands, 300! ILists are possible. This diversity in the ILists makes the decrease of τ_{neg} more and more difficult. The scalability of the negative selection process is compromised with the increase of the systems' size. A more general approach to perform the selection of the repertoire of detectors in bigger systems is required. This will be the issue of the discussion of the next section.

4.3.2.3 Limited connectivity allows education in bigger systems

Up until now, it was considered that agents interact with all the agents from the opposite type. The approach considered here assumes that each detector interacts only with a fraction of all the ligands in the system. Positive education ensures that a network of interactions is established that guarantees that all agents are continually interacting, while negative selection orders the ligands in ILists.

To study the effect of limited connectivity, the system with 300 ligands presented in the previous section, in which τ_{neg} does not decrease is selected. The composition of the system was the same of the last section, but different connectivities for detectors were considered: k=300, k=200, k=100, k=60 and, finally, k=15. The decay of τ_{neg}/τ_{neg_I} as a function of the interactions in each system is presented in Figure 4.20.

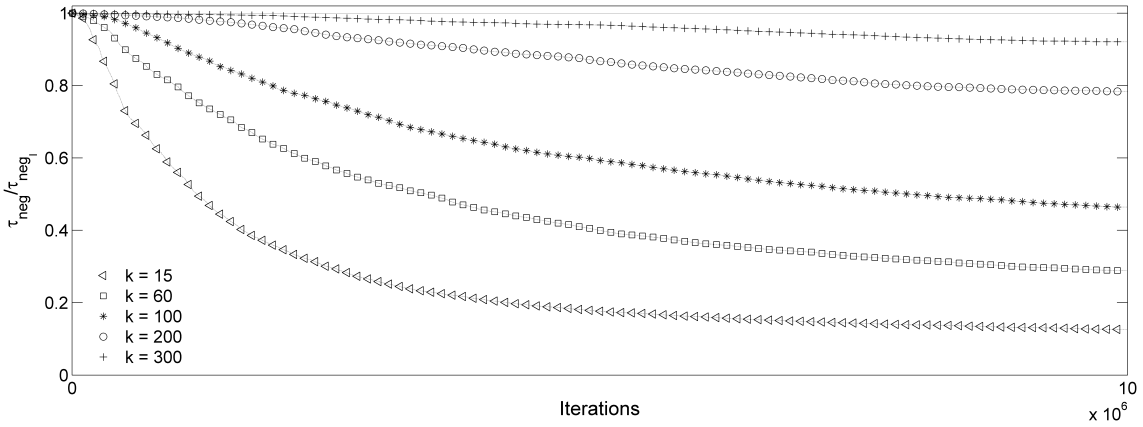


Figure 4.20: τ_{neg}/τ_{neg_I} decay for a 300-agents per type system and different connectivities as a function of the iterations.

The effect of the reduced connectivity on the decay of τ_{neg} is remarkable. If it is considered that each detector can interact with 5% of all presenters (k=15), τ_{neg}/τ_{neg_I} decreases to 0,13±0,09 of its initial value. Higher connectivity implies more ligands to order and, consequently, smaller decreases in τ_{neg}. The connectivity reduction ensures that the education process is not made more difficult with the increase in the size of the systems. Hence, the scalability of the education process is guaranteed with the selection of the appropriate connectivity in each system according to the size of the system.

4.3.2.4 Negative education prevents stable conjugations

From the previous results it is clear that τ_{neg} decreases during the negative selection process, even for big systems. Here, the impact of the negative education on the ordering of the ILists will be analyzed.

For simplicity, systems with 2 and 3 clusters were analyzed. The composition of the systems was the same as considered before: 60 agents per type equally divided into clusters, and with the same definition for detectors and their receptors. However, instead of considering an established computational time - $1x10^7$ iterations, as previously -, the education process finishes when τ_{neg} achieves an established threshold value - τ_{ed}=450 - equal for both systems. Forty independent educated populations were educated in each system. For each population, the number of detectors that placed ligands of presenters that have higher affinity for them in each IList position is determined. According to this value, the probability of one arbitrary detector placing a ligand of a presenter that has higher affinity with it, P, in a given position of the IList, POS, is represented for both systems (Figure 4.21). The same probability is determined for a detector that does not undergo the education process for systems with 2 and 3 clusters. All probabilities are shown with the error bars represented with shaded areas.

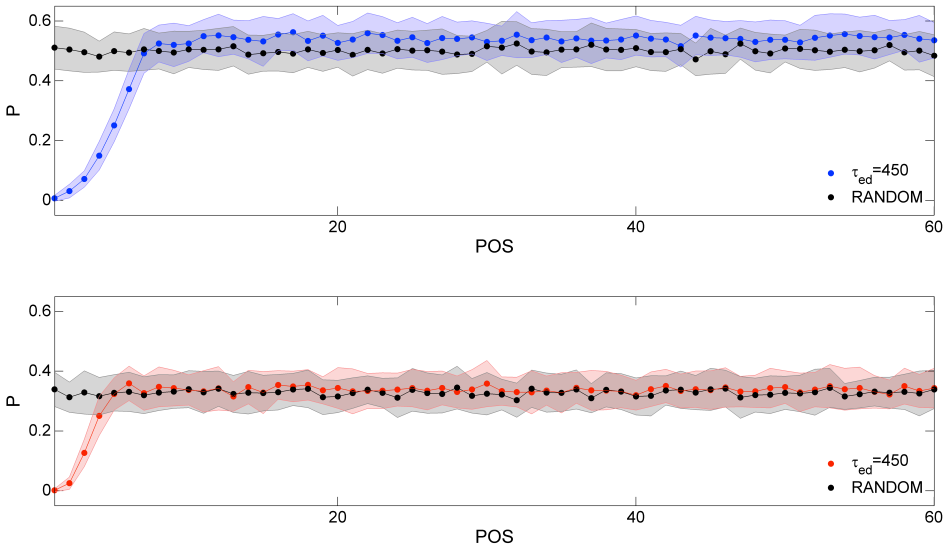


Figure 4.21: Probability of a detector of an arbitrary population avoiding a ligand displayed by a presenter having high affinity for it as function of the position of the IList, POS, in a 2 and 3-cluster system (top and bottom, respectively) and with an educated and no-educated repertoire.

Detectors that undergo the negative education process have probability almost zero of placing a ligand of a presenter that has high affinity for them in the top position. For every 150 educated detectors, there is always 1 detector that places in the top position a ligand that has high affinity for it in a 2-cluster system. For a system with 3 clusters, this value decreases to 1 detector in every 588. Moreover, the associated variability is extremely small when compared with the remaining positions in the ILists. This result is remarkable when compared with systems that did not undertake the education process. In random systems, for every 2 or 3 detectors in the repertoire, 1 detector places a ligand that has high affinity for it in the top position, in a 2-cluster or 3-cluster system, respectively. The probability is around 50% or 30%, and it is approximately equal for all positions in the IList.

Another interesting analysis concerns the range of educated positions in ILists. The number of educated positions is defined as the number of positions until the slope of the function P(POS) in Figure 4.21 is maximal. According to this definition, the education of 3 top positions in ILists is enough to decrease τ_{neg} to 450 in a system with 3 clusters (Figure 4.21), while in systems with 2 clusters 6 top positions are required. In addition, these positions have small associated errors, which indicates that the ILists are more uniformly ordered in the educated positions.

The results presented here demonstrate that detectors undergoing this process have ligands of presenters that have low affinity for them in the top positions of their IList, and, consequently, a frustrated conjugation will be established. In the next section, the possibility of increasing the range of educated positions will be investigated.

4.3.2.5 Extensive education increases the ordering of ILists

The previous results showed that the top positions of ILists can be ordered by means of a negative education process. However, the education process in the previous section was finished before 1x10^{7}iterations. Is there any difference in the ordering of the ILists if a more exhaustive education process?

In order to analyze the effect of an extension of the education process on ILists, systems with 60 different ligands equally distributed into 3 clusters were simulated, using different computational times. As in the previous section, 40 educated populations were obtained and τ_{ed} was reduced to 150. The probability that an arbitrary detector places a ligand of a presenter that has high affinity to it as function of the position of ILists, for these more lengthy education processes are shown in Fig-

ure 4.22. This probability is compared with the same probability calculated for systems educated with τ_{ed}=450.

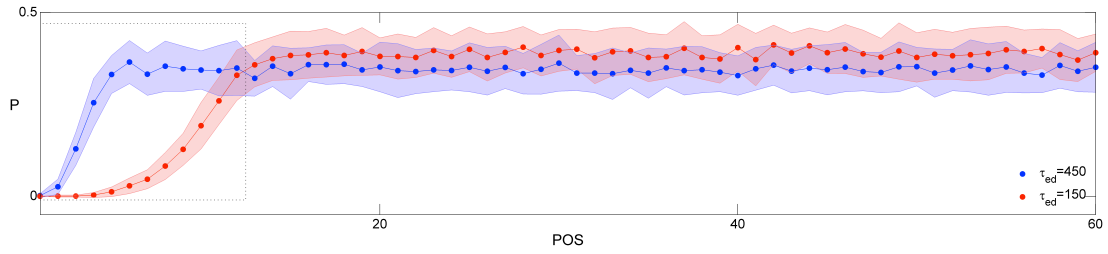


Figure 4.22: Probability of a detector of an arbitrary population of having ligands displayed by presenters having high affinity for it as a function of the ILists positions, POS, for a two educated repertoires of detectors with τ_{ed} (τ_{ed}=150) and (τ_{ed}=450).

The value of τ_{ed} required in the negative education process has a crucial effect on the range of positions that are educated during the negative education process. A decrease of 300 iterations in τ_{ed} - from 450 to 150 - increases the number of educated positions from 3 to 11. Another interesting result is that in a sample of 40 educated populations, none of the detectors placed a ligand of a presenter that has higher affinity for it in the top position. The probability is much smaller, at least one order of magnitude smaller, in the first six positions of the IList, in systems educated with τ_{ed}=150. This probability remains smaller in the next six positions. However, the smaller probability in the 12 top positions is counterbalanced by an increase of the probability in the remaining positions. These results support that extensive education processes increase the ordering on ILists. Detectors that undergo extensive education processes have higher probability of avoiding ligands of presenters that have higher affinity for them. In the next section another strategy to increase the ordering of ILists will be discussed.

4.3.2.6 Ordering of ILists is facilitated by the introduction of clusters

An extensive education can increase the order in ILists for a given system. In this section the relationship between the ordering of the ILists and the number of clusters will be discussed.

In order to do that, different configurations, in which the 60-agents per type were equally divided into 2, 3, 4, 6 and 10 clusters were considered. In each configuration 40 populations were educated with the τ_{neg} achieved in Table 4.1. The probability that an arbitrary detector places a ligand of a presenter that has high affinity for

it as function of the position of ILists was represented for all the systems. The same probability was determined for 40 populations of random detectors with the same system's composition. For each system, both probabilities were compared in Figure 4.23. The vertical dashed line represents the region in which ligands with the highest affinity for each detector should not be present. For instance, for a system with 2 clusters, no ligand presented by agents in the first cluster should appear in the first half of the subtype I detectors ILists. This value decreases to 60/3 for a system with 3 clusters.

An increase in the number of clusters corresponds to a decrease in the number of agents in each cluster. Hence a small number of agents has maximal affinity for each cluster of detectors, and, consequently, the probability that a detector places a ligand that has maximal affinity for it in the forbidden range also decreases. In a system with 2 clusters it is around 0.5 while in a 10-cluster system it is only 0.1; thus, the negative education process is less complex in a 10-cluster system. Another consequence of the introduction of clusters is that, different lifetime conjugations will be established, and any longer conjugation signals an incorrect ligand placed in the top positions of a detector's IList. Thus, for each longest conjugation, the corresponding detector is deleted and replaced by a new incoming detector.

It is also interesting to notice that the small probability of placing ligands that have maximal affinity for a detector is counterbalanced by a higher probability in the remaining positions. The more effective this difference, the more frustrated the dynamics. This structure ensures that detectors and presenters never establish stable conjugations and the system never reaches stable configurations.

In order to clearly see the result of the negative education, the probability that a detector places ligands of presenters that have maximal affinity to it only for the top position (P_{TP}) as a function of the number of clusters (N_C) is presented for a random (RAND) and an educated (EDU) detector, as well as its theoretical value (THEO) calculated for an arbitrary population of detectors by the ratio:

$$P_{THEO} = \frac{N_{HA}}{N_T} \tag{4.3}$$

between the number of ligands that have high affinity for a given detector, N_{HA}, and the total number of ligands in the system, N_T(Figure 4.24).

Educated systems have probability almost zero of placing in the top position a ligand of a detector that has maximal affinity for it, for every systems' composition.

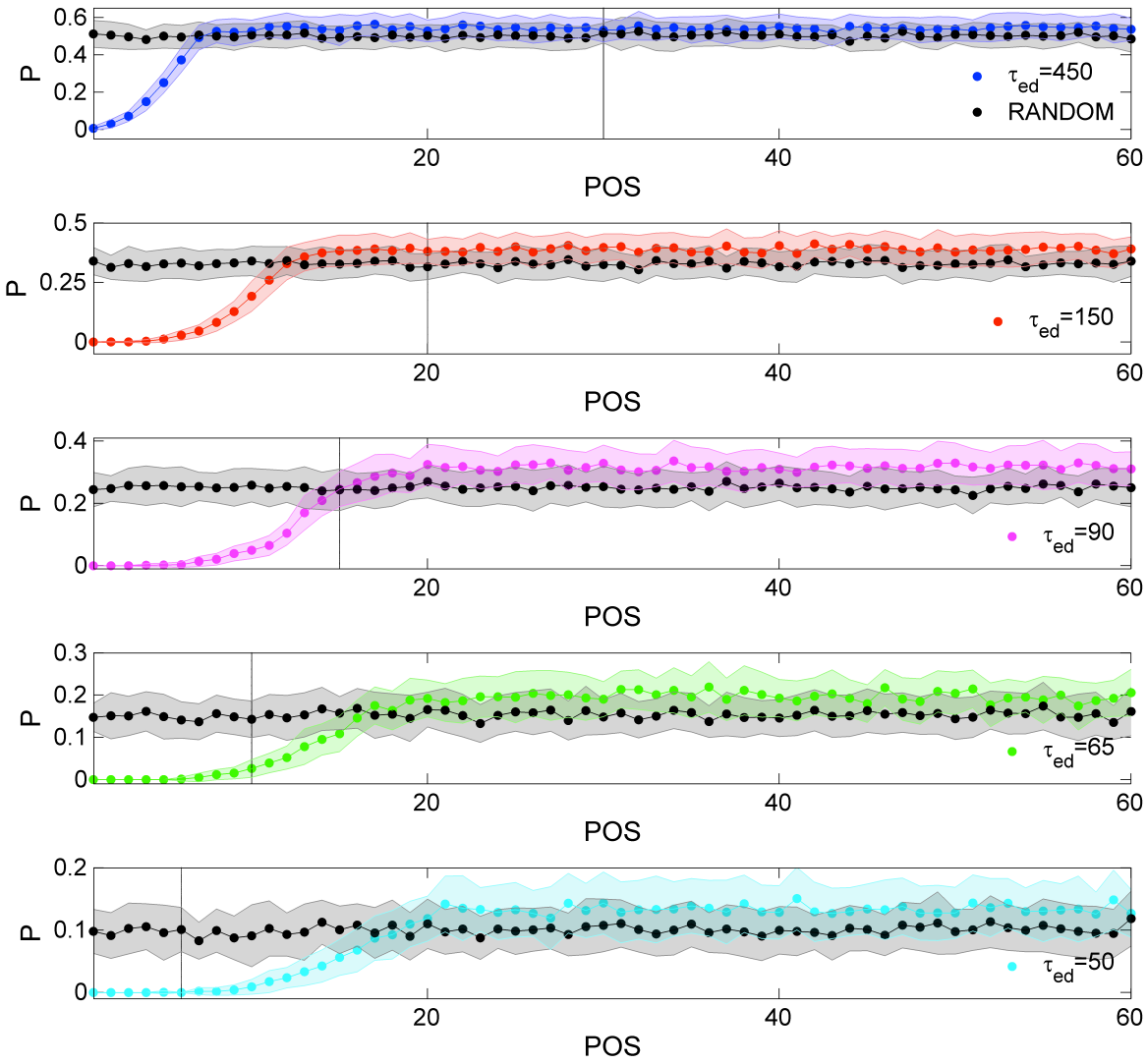


Figure 4.23: Probability of a detector of an arbitrary population of having a ligand of a presenter that has higher affinity for it, P, as a function of the ILists positions, POS, for systems with 2, 3, 4, 6 and 10 clusters, from the top to the bottom, respectively.

Moreover, systems with more than 2 clusters never placed a wrong ligand in the top position of its IList. For random systems this probability decreases with the introduction of clusters, as predicted by the theoretical value.

Also the effect of the number of clusters in the number of educated positions, N_{EP}, is analyzed as a function of the number of clusters, N_C, for an equivalent

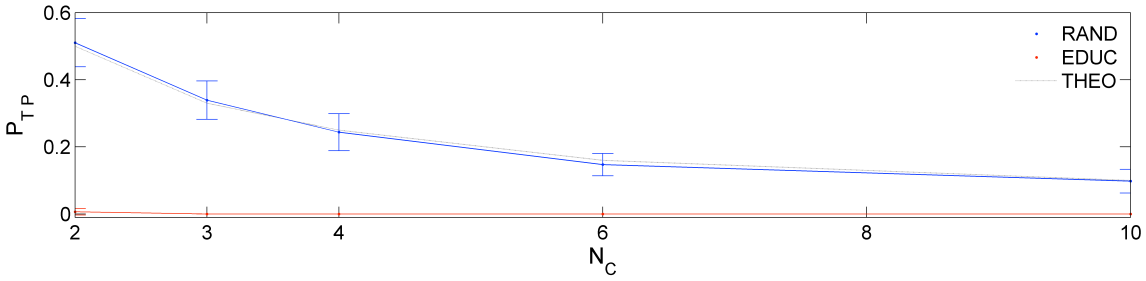


Figure 4.24: Probability that a detector places ligands of presenters that have maximal affinity to it on the top position, P_{TP}, as a function of the number of clusters, N_C, for an arbitrary (RAND) and an educated (EDU) detector, as well as its theoretical value (THEO).

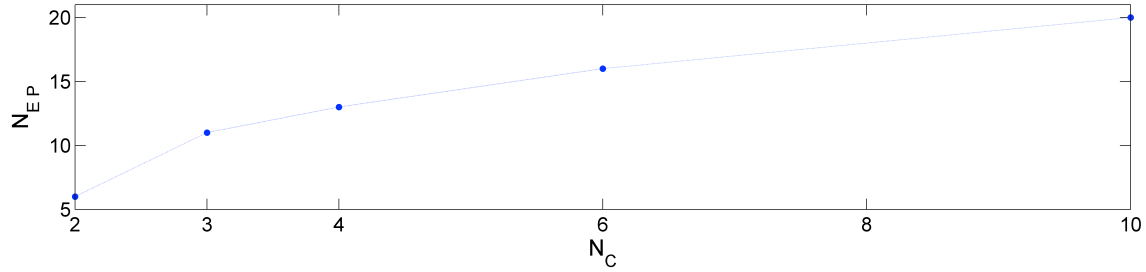


Figure 4.25: Number of educated positions, N_{EP}, as a function of the number of clusters, N_C.

education time (Figure 4.25). On one hand, the increase of the number of clusters decreases the range of positions in which the ligands of the detectors that have maximal affinity for each detector, should be avoided - this range ends with the vertical line represented in each plot. Despite the fact that a smaller number of positions should be educated to avoid maximal conjugation lifetimes, with the increase of the number of clusters, for the same computational time the number of educated positions increases with the increase of the number of clusters. Actually, this is an expected result, due to the decrease in the complexity of the education process due to the increase of the number of clusters. As already mentioned, the conjugations established in systems with higher number of clusters have smaller durations and the decision dynamics that is generated is more frustrated.

From these results it is clear that the introduction of clusters reduces the complexity of the education process, which is corroborated by the τ_{neg} decrease and by the ordering of the ILists. However, it is also important to bear in mind that the increase in the number of clusters reduces the difference between the probabilities in educated and in random systems. This is due to the fact that random systems

with a big number of clusters have a small probability of placing a "wrong" ligand in the top positions.

The results obtained in the previous sections suggest that the education process really increases the frustration in the system. Can this be visible in the dynamics of the system? This is the question that will be answered in the next section.

4.3.2.7 Frustrated Conjugations depend on the negative education process

In order to analyze the effect of the negative education in the dynamics, different systems were simulated in the monitoring phase. The dynamics generated by an arbitrary population of detectors educated with different τ_{ed} values. Both dynamics were compared with the dynamics generated by an arbitrary population of detectors that do not undergo the education process. A 3-cluster system with 60 agents of each type equally distributed and with the typical composition of ligands and receptors is considered. All systems were simulated for the same computational time, 10000 iterations.

The decay of τ_{neg} during the education of the 40 populations as function of the maximal number of iterations required to accomplish the process is represented (Figure 4.26 top). Letters A, B and C point the end of the education process in the systems considered: A corresponds to random populations of detectors, while B and C correspond to educated populations after τ_{ed}=450 and τ_{ed}=150, respectively. The generic histograms that represent the probability of each presenter establishing a conjugation with a lifetime longer than τ are presented for all systems (Figure 4.26 bottom). Vertical dashed lines represent the values of τ_{ed} used to stop the education process.

The computational cost of the education process depends on the τ_{ed} chosen to finish the education process. The education of a population of detectors with a τ_{ed}=450 takes less than one tenth of the iterations that are required to finish the process with a τ_{ed}=150. Lowering τ_{ed} increases the number of iterations required to accomplish the education process, but also increases the frustration of the system after the education process.

In the monitoring phase, the probability of a given presenter to establish stable conjugations decreases with the decrease of the τ_{ed} used to finish the education process. In systems without education, all conjugation lifetimes are allowed; detectors placed all presenters' ligands in random orders. Hence, a large number of presen-

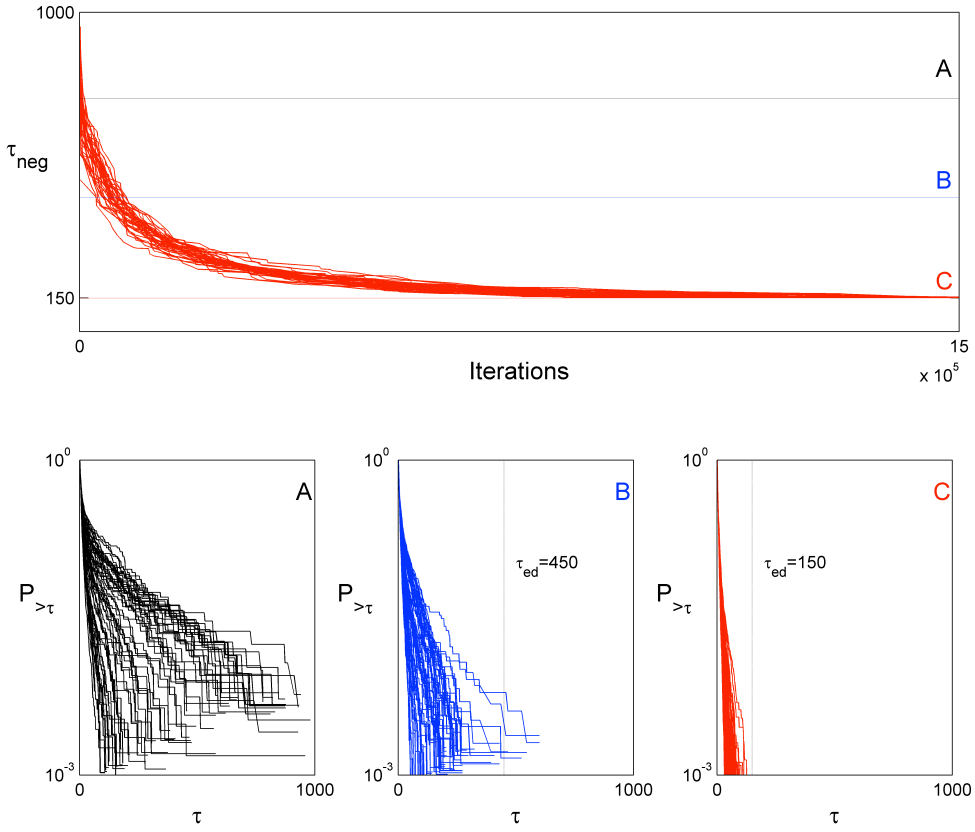


Figure 4.26: Top: The decay of τ_{neg} during the education of 40 populations as function of the maximal number of iterations required to accomplish the process. Letters A, B and C point the end of the education process in three different systems. Bottom: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$ for each presenter and (A) for a random system and for detectors educated with thresholds (B) τ_{ed}=450 and (C) τ_{ed}=150.

ters frequently establish long conjugation lifetimes with detectors (Figure 4.26A). For the educated systems the behavior is different (Figure 4.26B and C). Presenters and detectors engage in a decision dynamics in which the probability of a presenter establishing long conjugations decreases considerably. The education process is very efficient in increasing frustration. However, occasionally, some conjugation lifetimes exceed the value of τ_{ed} for which detectors are educated (Figure 4.26B). These events should be eliminated, because they could signal a triggering event and a response could be initiated against agents belonging to the system. How to eliminate false activations is the topic of the next section.

4.3.3 Education Process: Final Discussion

The education process is crucial in CFSs due to the fact that it is responsible for generating a maximally frustrated dynamics. The most important results can be summarized in two different parts which correspond to the positive and negative education processes:

Positive Selection(PS)

- Asymmetric systems converge from configurations with the same number of presenters and detectors of each subtype;
- PS reduces fluctuations on the number of detectors of each subtype;
- Maximally frustration dynamics takes place in systems with restricted connectivity if PS shapes the detectors' network of interactions, so that they continually interact with presenters.

Negative Selection(NS)

- The convergence of the education process is quicker in systems with more clusters;
- Restricted connectivity allows scalability of the education process;
- Stable conjugations are eliminated by NS;
- Extensive education processes increase the ordering of the detectors' ILists and increase the frustration of the dynamics;

The education process increases the global frustration of the dynamics that is generated in the system. It is interesting to notice that an educated repertoire of detectors can only be generated if both processes operate during the education process.

From a deeper understanding of the educated process emerged the role of both processes. PS operates to guarantee the interactivity of the detectors: it prevents them from not interacting. The NS process does not decrease the affinity of the interactions, as suggested in the literature, rather it reduces conjugation lifetimes

by eliminating detectors that do not frustrate the dynamics. These results suggest a new perspective on the function of both systems either in artificial immune systems models or in the immune systems.

4.4 Detection of Foreign Ligands

The relevance of the perfect discrimination in Immunology or in other fields is completely different. In Immunology, whether responses depends on discrimination between self and nonself and whether this can be perfect, is not consensual [3, 50, 51]. Textbooks refer that self/nonself discrimination is "excellent but imperfect" ([1], p. 71), leading occasionally to "reactions against self antigens" ([1], p.71).

Even if discrimination can not be perfect in the immune system, several other issues concerning its functioning remain without answer. In addition, in different fields like for example computer security, the relevance of the perfect discrimination between what belongs or not to the system is crucial. Thus, the study of systems capable of performing perfect discrimination is relevant. In this section questions concerning how perfect discrimination self/nonself in CFSs can be achieved will be discussed.

4.4.1 Simulations and Parameters

To investigate the performance of the detection of foreign ligands, 1000 invaders were introduced in systems with different number of clusters. Typically, 2 or 3-cluster systems were considered with 60 agents per type - the same systems discussed in the previous section for the education processes. Due to the fact that systems with different compositions have different τ_{ed}, the ratios were calculated for different values of τ in each system. Three different lifetimes were analyzed corresponding at 15%, 30% and 60% of the τ_{ed} of each system - denoted by τ_1, τ_2 and τ_3, respectively. Furthermore, all conjugations longer than τ_{sep}, τ_{sep}=1.5×τ_{ed}, were destroyed. This makes the dynamics more uniform. The several parameters used in the detection analysis are presented in Table 4.2.

Table 4.2: Parameters Considered in Simulation.

Cluster	Agents per Cluster	τ_{ed}	τ_1	τ_3	τ_{sep}
2	30	450	68	270	675
3	20	150	23	90	223
4	15	90	14	54	135
6	10	65	10	39	98
10	6	50	8	30	75

The extended repertoire of detectors is usually composed by 40 educated populations (i.e. 60×40=2400 detectors), which interact with the presenters. The anergy characteristic time was τ_{an}= 2. In order to perform the detection stage it is necessary to perform the calibration stage, so that the "normal" profile of interactions is established for each presenter. To to this, 1000 independent systems without perturbation were simulated, during 10^4 iterations, - as many as later used during the detection stage. The same procedure was repeated with introduction of foreign ligands. In this section, the comparison between the frequency of conjugations lasting longer than τ established by presenter P_i - $f_{i,>\tau}$ - is compared not with its reference $f^o_{i,>\tau}$ but with the maximal value of $f^o_{i,>\tau}$ registered in the calibration stage for all the presenters. This corresponds to WS frequencies. The detection ratio calculated to establish the detection criterion is given by:

$$\mathcal{R}_{fl} = \frac{f_{i,>\tau}}{Max\{f^o_{i,>\tau} \times F\}} \tag{4.4}$$

the tolerance parameter F being equal to: F=1.01. This was chosen to allow detection with perfect tolerance against self. Any changes in these conditions is presented in detail in the beginning of each section.

4.4.2 Numerical Results

4.4.2.1 Detection of foreign ligands in educated populations

In section 2.2 it was shown that all intruders could be potentially detected in CFSs. In order to investigate the number of invaders that escape, 1000 invaders were introduced in the 2-cluster systems presented before with a restriction on the repertoire of detectors. The same simulation was performed for non educated populations. It is assumed that an invader is a presenter that displays a ligand never presented during the education process.

For both populations of detectors - with and without education- the detection ratios are determined and presented (Figure 4.27). Ratios obtained for the educated population are presented in blue, while ratios obtained with detectors with random ILists are presented in black. The same markers correspond to the same τ.

As expected, the education process is crucial to perform detection of foreign ligands. In systems without education 980 intruders escape detection (at τ=150). This value decreases to 331, when one educated population of detectors in the repertoire.

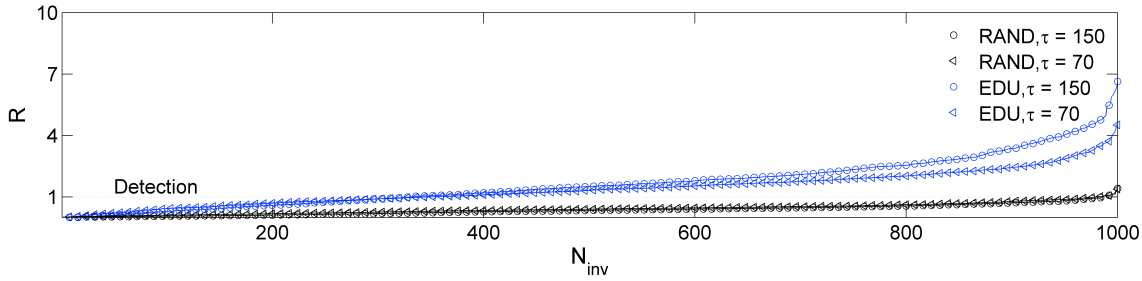


Figure 4.27: Detection ratios, $\mathcal{R}$, for 1000 foreign ligands, N_{inv} , at τ=70 and τ=150, in a 2-cluster system, 2C, and 1 population of detectors.

By adding another cluster, 216 invaders escape detection (Figure 4.28).

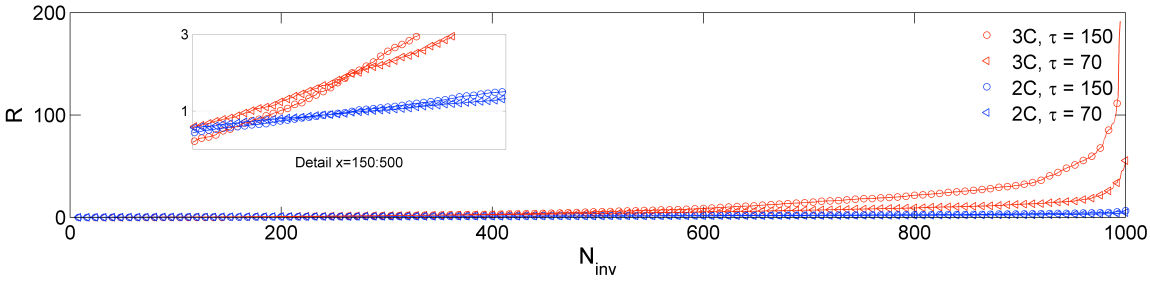


Figure 4.28: Detection ratios, $\mathcal{R}$, as a function of the foreign ligands simulated, N_{inv}, at τ=70 and τ=150, for systems with 2 and 3 clusters (blue and red, respectively).

Figure 4.29 shows typical histograms obtained in the monitoring phase for two different invaders, for a detection and a non-detection events. For τ=150 the values used to calculate the detection ratio, $\mathcal{R}$, are pointed in each case.

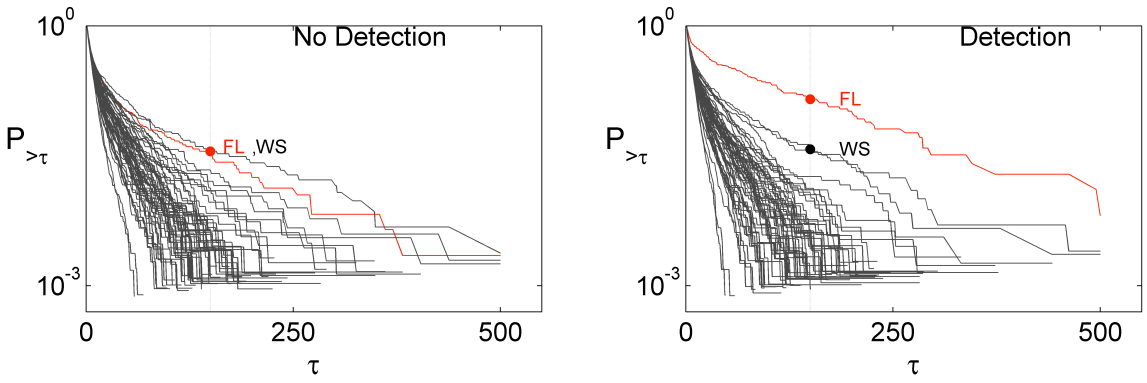


Figure 4.29: Generic histograms obtained in the monitoring phase for two different foreign ligands. FL and WS point the values used for calculating the detection ratio $\mathcal{R}$ at τ = 150.

Despite the effect of the education or the system considered, perfect detection

of foreign ligands can not be successfully achieved by a single population of detectors. To achieve perfect self/nonself discrimination two fundamental mechanisms are required in monitoring the dynamics. They will be the issue of the next sections.

4.4.2.2 Anergy as a mechanism that maximizes frustration

In CFSs each detector that establishes a longer conjugation becomes anergic or unresponsive and it is replaced by an equivalent. This mechanism ensures that detectors that establish short conjugation lifetimes remain in the system, while detectors that establish long conjugation lifetimes become unresponsive and are replaced. Hence, the surveillance is maintained by an extended repertoire of detectors, and the probability of a long conjugation is small.

Anergy was introduced in the monitoring phase and the systems of the last section were simulated: a system without education and two educated ones (τ_{ed}=150 and τ_{ed}=450). In order to better understand this mechanism, two different sizes of the repertoire of detectors were used, one with five and another with twenty populations of detectors - N_{pops}=5 and N_{pops}=20, respectively. The dynamics that is generated in the monitoring phase with the introduction of anergy is presented in Figure 4.30. In order to simplify the analysis, typical histograms obtained without anergy (N_{pops}=1) are also represented. While each column illustrates the impact of anergy with the same size of the repertoire in different systems, each row shows the impact of the size of the repertoire in the same system.

Anergy increases frustration in the monitoring phase: conjugation lifetimes are reduced, as well as the dispersion in the lifetimes. If several detectors establish long conjugations, this signals a modification in the system and it is not the result of a weak education. In the next section, the second main mechanism that allows perfect self/nonself discrimination will be presented.

4.4.2.3 Differentiated activation ensures perfect monitoring

Anergy increases the frustration of interactions between agents, which is crucial to ensure detection of foreign ligands. However, frustration is not uniform for all presenters. They can have different probabilities of establishing longer conjugations, which is expressed by a different range of $P_{>\tau}$ for a given τ (Figure 4.31). The larger the τ, the widest the range of $P_{>\tau}$ with occurrences, as shown by the vertical dashed line in τ=70. Also, it is possible to verify from the histogram that events

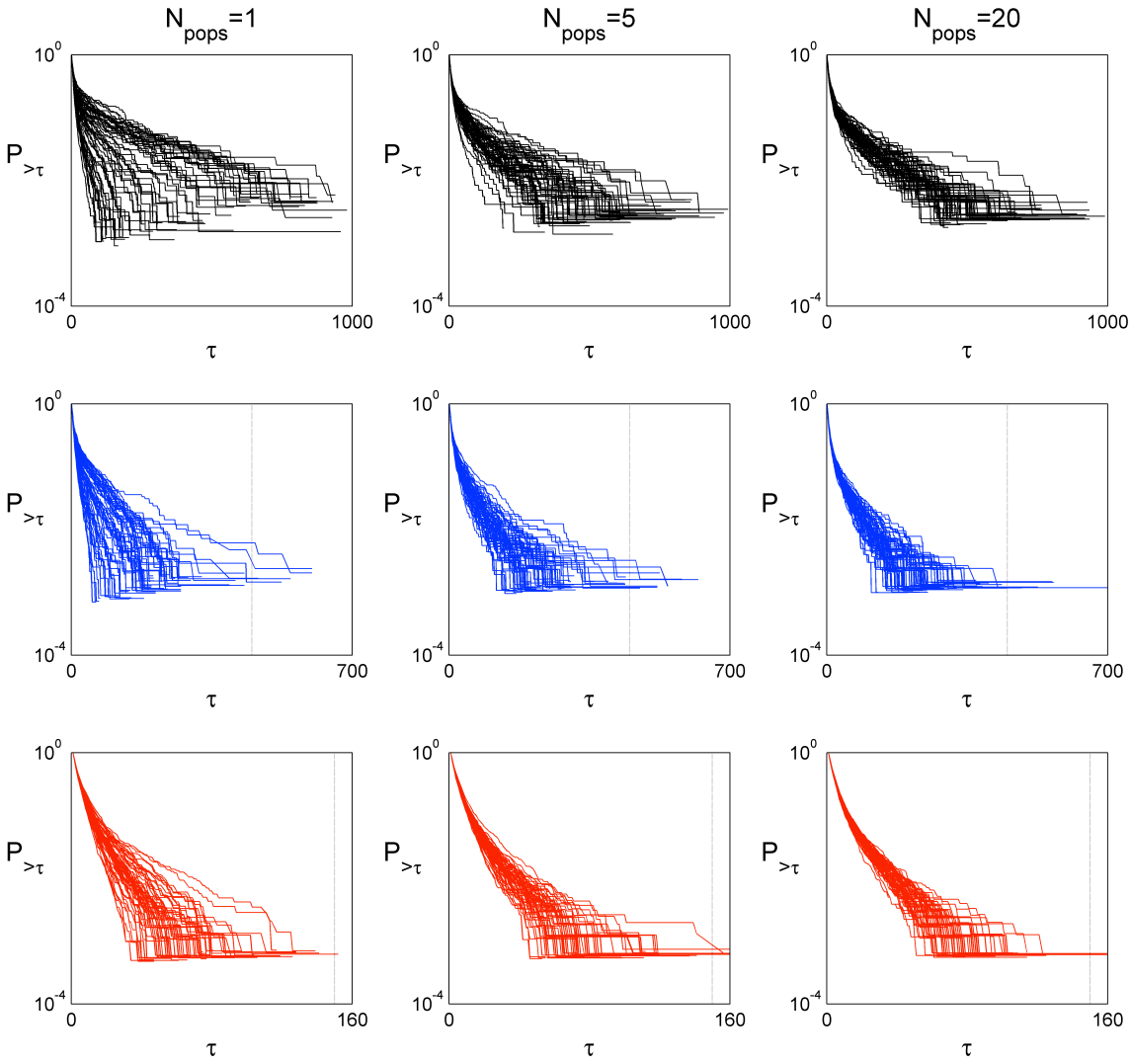


Figure 4.30: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$, for each presenter, and (Black) for detectors with random ILists and (Blue and Red) with populations of detectors educated at two different τ_{ed} values, pointed out with vertical lines. While each column illustrates the impact of anergy with the same size of the repertoire in different systems, each row shows the impact of the size of the repertoire in the same system.

with lifetimes longer than the education threshold - 400 in this system - occur in the monitoring phase.

This heterogeneity in conjugation lifetimes is enough to compromise the prompt attacks of invaders with total tolerance towards self. Actually, the second mechanism proposed takes advantage of this heterogeneity due to the education process. In

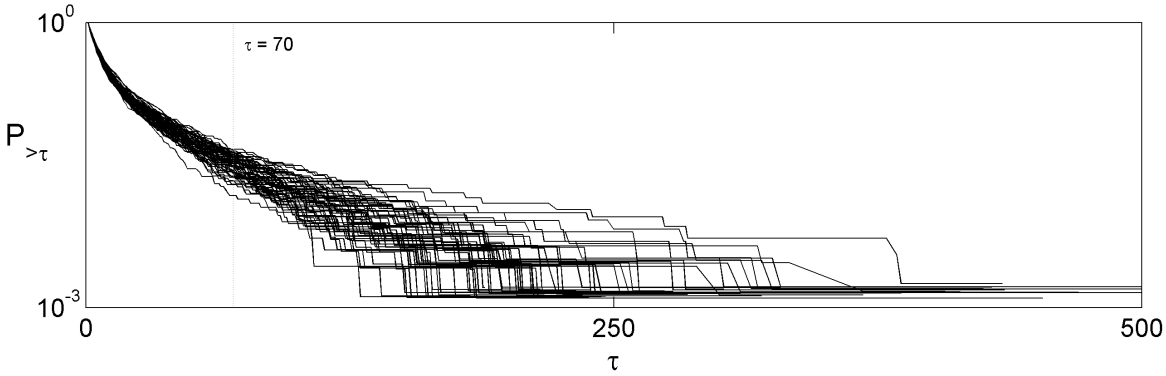


Figure 4.31: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$, as a function of τ during the monitoring phase. The vertical line highlights results at a fixed lifetime τ=70.

CFSs each presenter selects its activation threshold in a calibration phase - $f^{o}_{i,>\tau}$ which is proportional to $P_{i,>\tau}$. This differentiated response is called costimulation.

In order to establish the activation threshold, 1000 simulations were performed in the absence of perturbations. It is considered a 2-cluster system and a repertoire of 40 populations with τ_{an}= 2. The lifetime analyzed was τ=70. Figure 4.32A presents the average value of $P_{>\tau}$ for all simulations and its value in a specific system as a function of the presenter - with blue and black dots, respectively. Also shown is, the maximal value of $P_{>\tau}$ - red dots - together with the system considered (Figure 4.32B). To simplify the comparative analysis, the respective histogram of each case is included. All histograms have the same scale in both axes.

It is clear that the value above which each presenter should trigger responses is the maximal value of $P_{>\tau}$ that is registered in the calibration stage. If the average is considered as threshold, 30% of the presenters could be wrongly activated against the agents of the system. Notwithstanding the average can not be used as activation threshold, it indicates an interesting aspect of the dynamics. Despite fluctuations, all presenters have a similar average value for $P_{>\tau}$. This indicates that all the presenters are almost equivalent for an arbitrary large calibration stage. It should be expectable that for an infinite window of calibration, the activation threshold will be similar for all the presenters.

In the monitoring phase, presenters with $\mathcal{R}\geq$1 will trigger a response (Figure 4.33). To verify the effect of the introduction of an intruder on the profile of $P_{>\tau}$ the first presenter displayed a foreign ligand, which had never been presented during the education phase. The frustration of the conjugations decreases

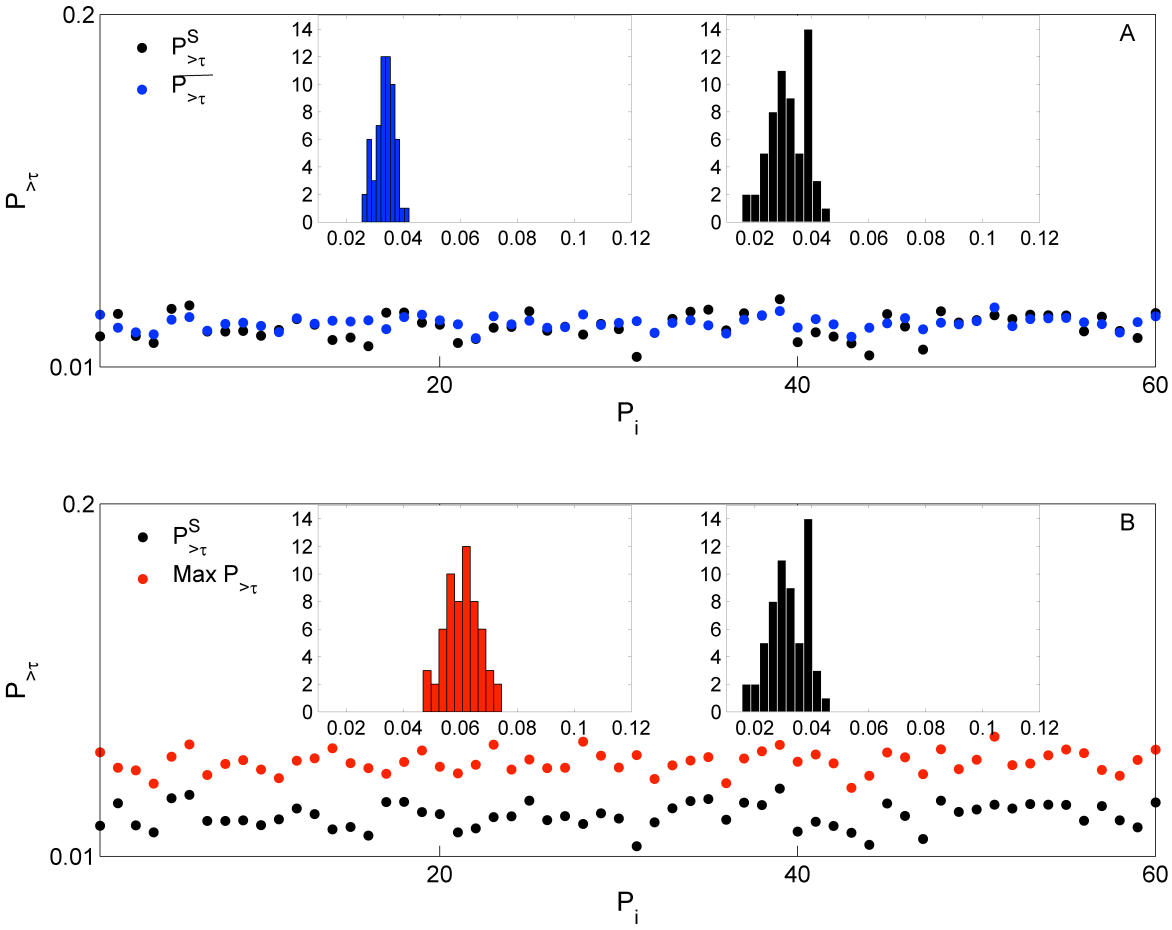


Figure 4.32: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$, for the several presenters and calculated at τ=70. (A) Blue dots represent the average of the $P_{i,>\tau}$ values registered for each presenter, during the calibration phase and black dots represent the same quantities for a given typical system. (B) Red dots represent the maximal $P_{i,>\tau}$ value registered for each presenter, during the calibration phase and black dots the same as before. Histograms in inner boxes group all the information for the corresponding plots.

substantially for this presenter, its $P_{>\tau}$ increased 63.7% when compared to with its activation threshold. It is also important to notice that $P_{>\tau}$ is below the activation value for all the other presenters.

This is an example of perfect detection of foreign ligands with perfect tolerance towards the agents of the system. The costimulation mechanism provides a differentiated activation. For the same $P_{>\tau}$, some presenters deliver activation signals and trigger a response, while for others no responses are signaled. In the next section,

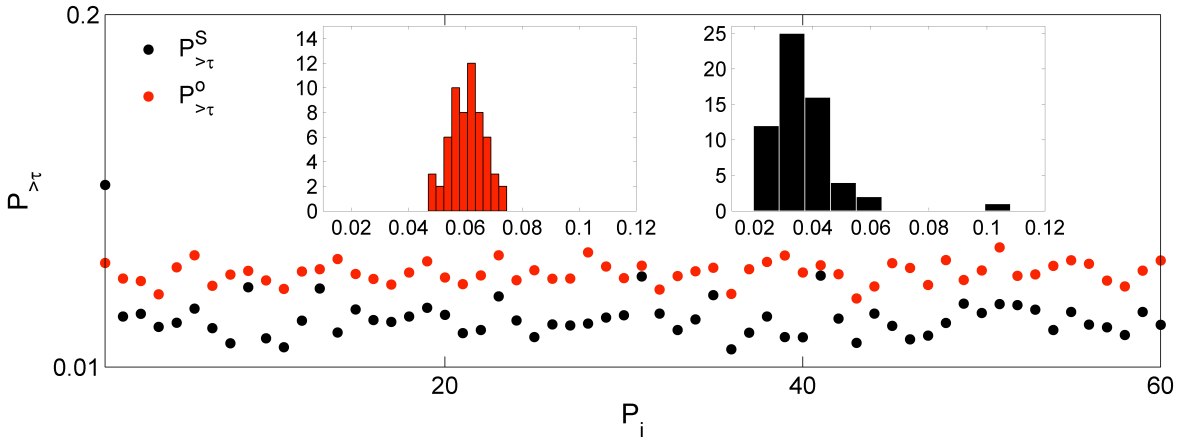


Figure 4.33: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$, for the several presenters, calculated at τ=70. Red dots represent the maximal value registered during the calibration phase and black dots represent the same quantities when a foreign ligand is introduced as presenter 1.

the performance of the detection of foreign ligands will be presented, considering anergy and costimulation.

4.4.2.4 Anergy and costimulation provide perfect discrimination self/ nonself in educated systems

After the discussion about anergy and costimulation, the performance of the detection of foreign ligands will be tested, with the introduction of both mechanisms. In order to do that, simulations were repeated for different sizes of the repertoire of detectors, 1, 3, 5, 10, 20, 30 and 40 populations of educated detectors in the 2-cluster system presented were considered. All simulations were performed during 10000 iterations with populations of educated detectors (τ_{ed}=400), considering τ_{an}=2. In each system, 1000 invaders were introduced and the detection ratio was calculated. It is important to notice that the ratios are calculated with the worst self, which corresponds to the maximal $f^o_{i,\tau}$, so this is the lowest possible ratio. The horizontal black line represents the value above which the invaders are detected. According to these ratios, the number of foreign ligands that escaped detection was determined and represented as a function of the repertoire size (Figure 4.34).

In systems with only 1 population more than 40% of the invaders escape detection. This value decreases exponentially to 0.1% when 20 populations are considered, and it is 0% for a repertoire with 30 or more populations. These results show that perfect detection of foreign ligands is possible, the probability of no detection (p_{ndet})

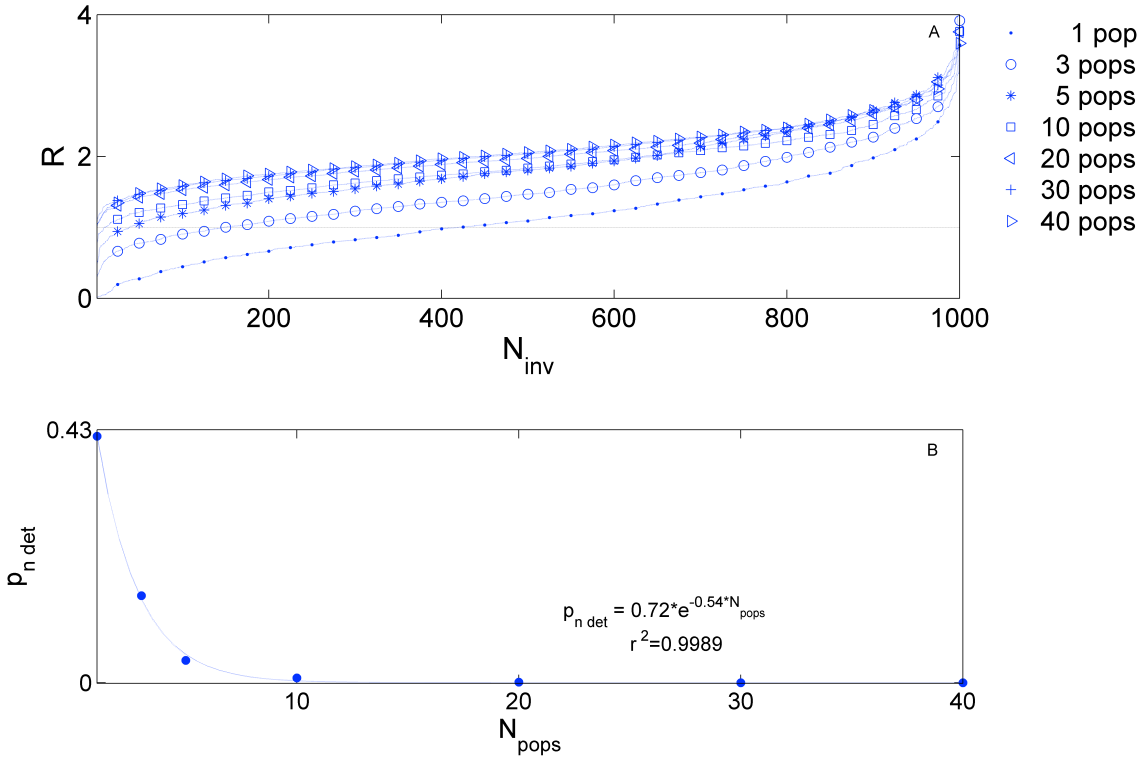


Figure 4.34: (A) Detection ratios, $\mathcal{R}$, calculated for 1000 foreign ligands, considering 1, 3, 5, 10, 20, 30 and 40 educated populations. (B) Probability of evasion p_{ndet} - no detection - as a function of the repertoire size, N_{pops}.

is below 1/1000. This result is only possible if detection is performed by a repertoire of detectors that undergo the positive and negative education process and costimulation and anergy are considered in the monitoring phase. This is the starting point to investigate the performance of the detection system in different conditions. In the next section, the impact of an extension of the education process is discussed.

4.4.2.5 Better education provides better detection

The result obtained for detection of foreign ligands in systems with extended populations of detectors suggests that systems without education can also perform detection of foreign ligands. Actually, this is not true (Figure 4.35). In systems without education all ligands are potential invaders because ILists order ligands randomly. Thus, all presenters have a high probability of performing long conjugations. In these systems, more than 97% of invaders escape detection and this value is independent

of the size of the repertoire. Not even anergy decreases this value.

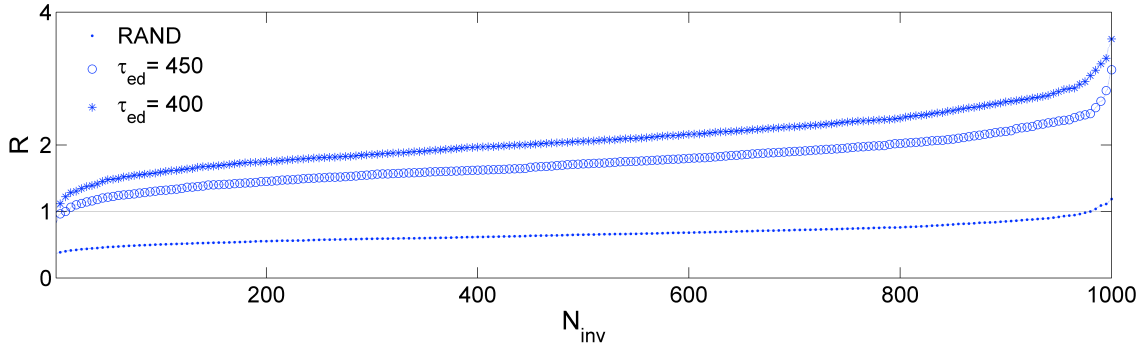


Figure 4.35: Detection ratios, $\mathcal{R}$, for 1000 foreign ligands, considering systems with 40 educated populations in the repertoire, non-educated (RAND) or educated with education thresholds τ_{ed}=450 and τ_{ed}=400.

Concerning detection in educated populations, the smaller τ_{ed}, the higher the ratio obtained and the smaller the fraction of invaders escaping detection. For the same size of the repertoire, the ratios obtained with $\tau_{ed} = 400$ are, on average, above the ones obtained with τ_{ed}=450. Also the performance of the detection system is different. While in the first system all intruders were detected ($p_{ndet} < 0.001$), for higher values of τ_{ed} 10 invaders escape detection (p_{ndet}=0.01). From these results it is clear that the ordering of ILists has a crucial importance in the detection of foreign ligands task and an extensive negative education processes promote better detections in the monitoring phase. In the next section the effect of the number of clusters in the detection will be discussed.

4.4.2.6 Detection becomes easier in systems with more clusters

As presented before, the increase in the number of clusters makes the convergence of the education process less complex. To evaluate the detection of foreign ligands performance with the increase of the number of clusters, 1000 foreign ligands were introduced, in systems with different compositions - 2, 3, 4, 6 and 10-cluster systems educated using the τ_{ed} in Table 4.2. In order to compare these systems, the detection ratios were calculated using time duration points.

Different repertoire sizes with 1, 3, 5, 10, 20, 30 and 40 populations of educated detectors were considered. To analyze the performance of the detection system, the the probability of invaders escaping detection, p_{ndet}, as a function of the repertoire size is represented, N_{pops}, in Figure 4.36 when the number of clusters was varied.

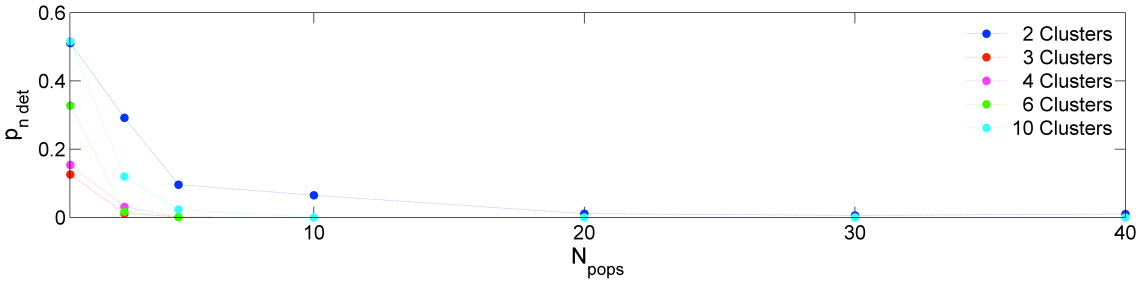


Figure 4.36: Probability of detection evasion, p_{ndet}, as a function of the repertoire size, N_{pops}, calculated at τ_1, and as a function of the number of clusters.

Figure 4.36 shows that increasing the number of clusters decreases the number of invaders that escape detection. For systems with more than 2 clusters, none of the invaders escapes detection when more than 5 populations compose the repertoire. For 2-cluster systems 10% of the invaders escape detection. However, this value decreases to zero if the extension of the education process increases, as presented before.

To evaluate the performance of the detection system, the analysis of detection ratios are presented for all systems and for two time durations τ_1 and τ_3 (Figure 4.37).

It is interesting to notice that for conjugations lasting at least τ_1 iterations, detection ratios are higher than in the systems with 3 and 4 clusters. For conjugations lasting τ_3 iterations, the result is different. The highest ratios are accomplished for the systems with 6 and 4 clusters. For conjugations lasting τ_3 iterations all systems have similar ratios, with exception of the 2-cluster system in which the ratios are smaller. To illustrate the dynamics for different systems, histograms of the maximal ratio obtained in each system are presented in Figure 4.38. A generic conjugation duration τ used for calculating the detection ratio is also clearly shown. Colored lines show the histogram for presenter presenting the foreign ligand, while black lines show the remaining presenters.

According to these results, it is possible to verify that the increase in the number of clusters favors the task of detecting foreign ligands in the system. The performance of the system is optimal in systems with 3 and 4 clusters, considering the number of invaders that escape and their detection ratios. However, perfect detection with smaller ratios can be obtained in a 6-cluster and a 10-cluster system, at τ_1. This result reinforces the remarkable ability to detect any foreign ligand in CFSs. Up until now all the results were obtained for systems with only 60 agents. In the next section, the detection in systems with a higher number of agents will be

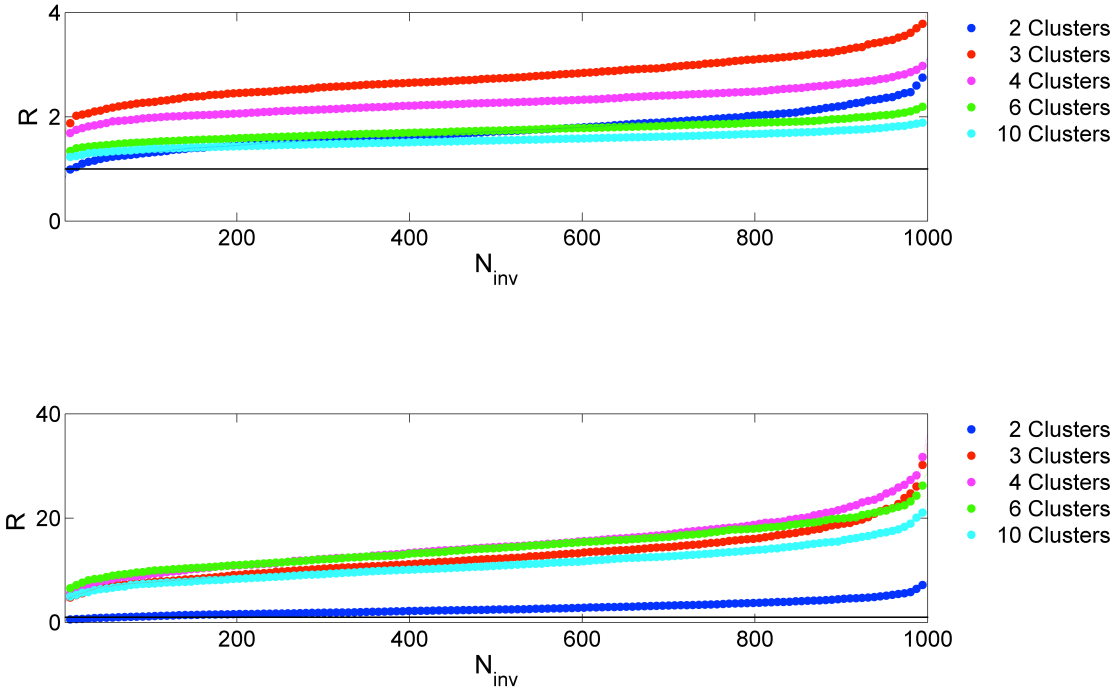


Figure 4.37: Detection ratios, $\mathcal{R}$, obtained for 1000 invaders, for systems with 2, 3, 4, 6 and 10 clusters and calculated at two different conjugation lifetimes τ_1(top) and τ_3(bottom).

discussed.

4.4.2.7 Perfect detection is also possible for systems presenting an arbitrary number of ligands

It was already shown that the education process converges independently of the number of agents in the system for detectors with limited connectivity. Here, the performance of the detection of foreign ligands in these systems will be discussed. The same 3-cluster system with 300 presenters and 300 detectors are considered. In order to study the performance of the detection system, 1000 foreign ligands were presented in a system with a repertoire of 40 educated populations of detectors with different connectivities - k=15 and k=60. Detection ratios, $\mathcal{R}$, between the invader and the worst self-presenter are shown in Figure 4.39, at τ_1 and τ_3, respectively.

Despite the number of agents, perfect detection is achieved when small connectivities are considered. With both connectivities none of the invaders escape detection,

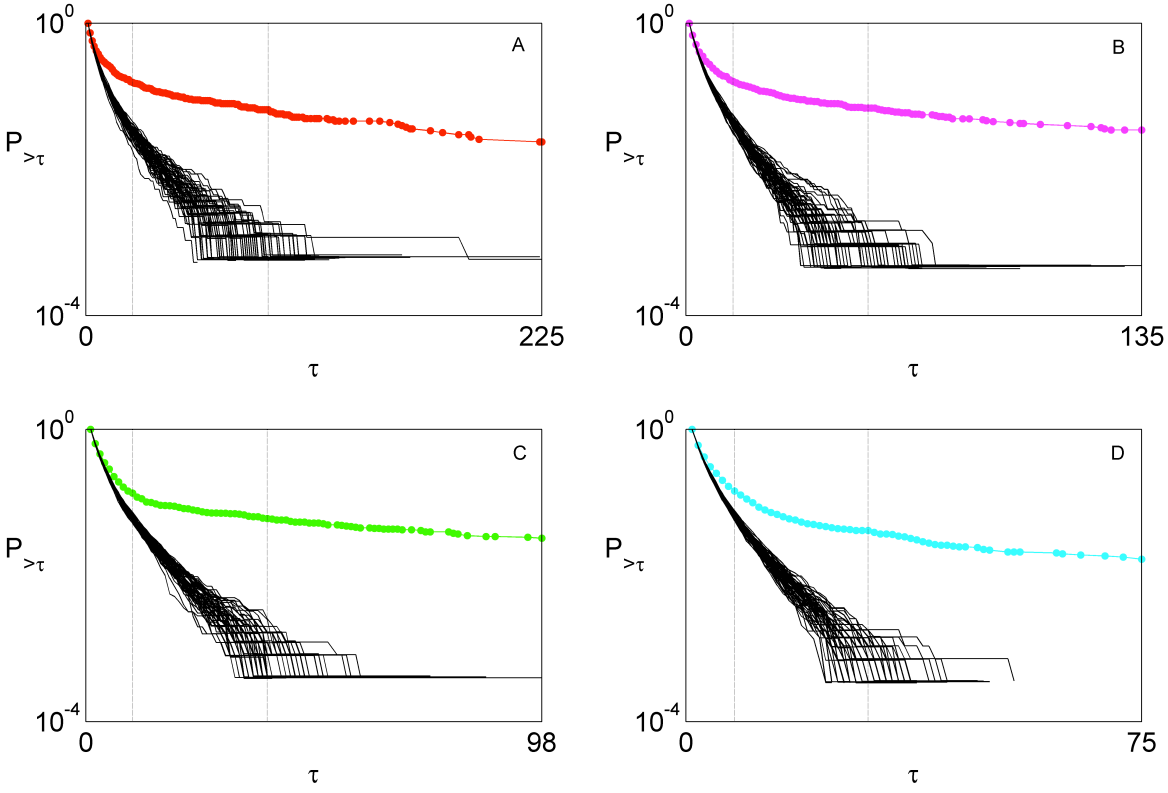


Figure 4.38: Probability of establishing a conjugation with a lifetime longer that τ iterations, $P_{>\tau}$ for each presenter and for foreign ligands leading to the maximal ratios in the results in figure 4.37 and for systems with (A) 3, (B) 4, (C) 6 and (D) 10 clusters. Vertical lines represent the conjugation duration τ at which detection ratios are calculated.

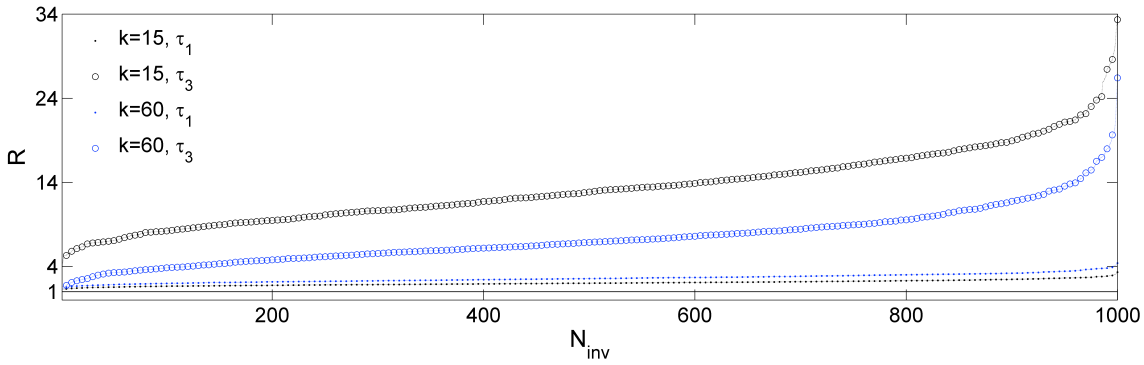


Figure 4.39: Detection ratios, $\mathcal{R}$, calculated as a function of the invader, N_{inv}, calculated at two different conjugation times, for a population with 300 agents of each type and two different connectivities 15 and 60.

for the two durations times chosen for the analysis; this shows that the analysis is robust relatively to the choice of the duration of the conjugation analyzed.

These results show that perfect self/nonself detection can be obtained in systems displaying an arbitrary number of ligands, if connectivity is restricted. Thus, there are no limitations on scalability of the detection task in CFSs.

4.4.2.8 Detection is more difficult in asymmetric systems

In order to study the impact of an inadequate positive education, a system with a different number of detectors on each cluster, - 48 in the first cluster and the remaining 12 in the second one, - was considered for a 2-cluster system. The negative education process was performed in this system and 40 populations were educated. After the education phase, 1000 invaders were introduced in the first and in the second cluster and denoted - inv_{C1} and inv_{C2}, respectively in Figure 4.40. The the fraction of invaders that escape detection as function of the size of the repertoire is presented.

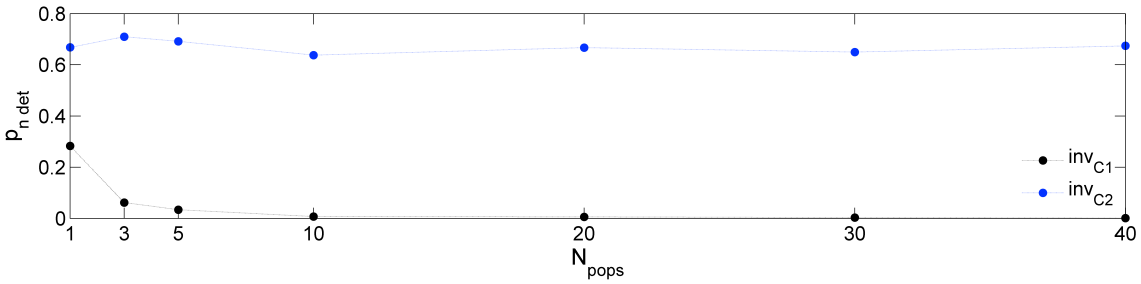


Figure 4.40: Probability of escaping detection when the foreign ligand is presented in the first or in the second cluster, inv_{C1} and inv_{C2}, as function of the number of populations in the repertoire, N_{pops}.

Detection of foreign ligands that are presented in the first cluster is easily accomplished. The result is completely different if the foreign ligand appears in the second cluster. The number of invaders that escape detection is higher than 60% and does not decrease with the increase of the repertoire of detectors. In order to better understand what happens in the dynamics, the histogram of conjugations by subtypes is presented (Figure 4.41). From the histogram it is clear than characteristic lifetimes change with the asymmetry in the number of detectors. Conjugations involving presenters from the second cluster are more frustrated than the equivalent ones in the first cluster. In order to be detected, an invader presented in the second cluster needs to perform a conjugation less frustrated than the one performed by

the presenters of the first. This is the reason why in this case, the detection is not accomplished. Because of the fact that the system is not symmetric, the agents of both clusters are not equivalent and the ratio calculated with the number of events for the worst self does not make sense. What makes sense in this case is to define the detection of foreign ligands by using the worst self of each cluster - denoted as WC in Figure 4.42 - instead of the worst self of all presenters - designated WS.

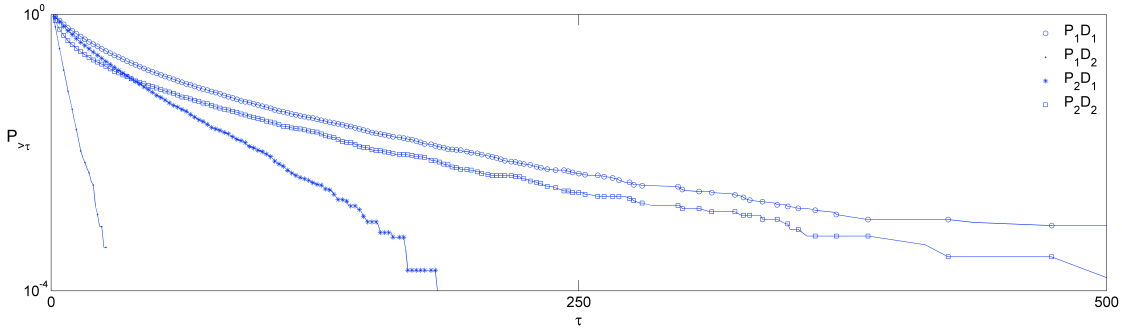


Figure 4.41: Probability of establishing conjugations lasting longer than τ iterations, $P_{>\tau}$ after the detection phase, and for pairs involving agents from the several subtypes. Conjugations involving presenters, P, from cluster i and detectors, D, from cluster j are represented as P_iD_j.

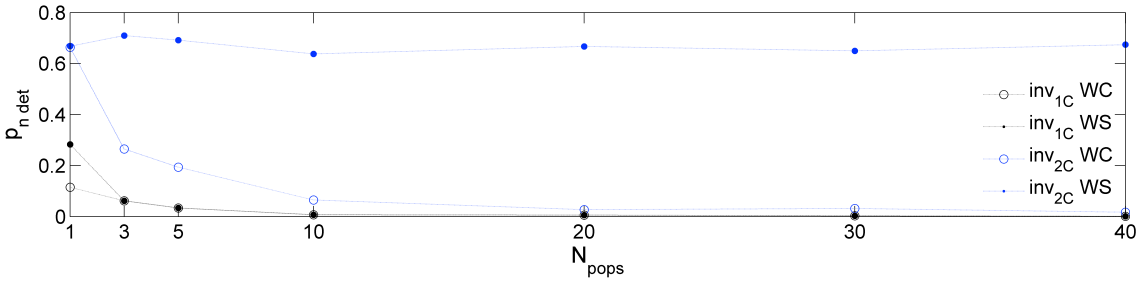


Figure 4.42: Probability of escaping detection when the foreign ligand is presented in the first or in the second cluster, inv_{C1} and inv_{C2}, as function of the number of populations in the repertoire, N_{pops}, and the definition used: the worst self in each cluster, WC, or the worst self from all presenters, WS.

If the foreign ligand is signaled with the worst presenter of each cluster, the number of invaders that escape detection in the second cluster decreases considerably. However, with 40 populations, 17 invaders escape detection (p_{ndet}=0.017). For the invaders presented in the first cluster, despite a fluctuation in the first point, the decay is equal with both criteria. Actually, this is the expected result because the maximal $f^o_{i,>\tau}$ used in the ratio is dictated for presenters of the first cluster - as shown in the histogram in Figure 4.41.

The positive education plays a role in the performance of detection systems. Despite being possible in asymmetric systems, detection of foreign ligands is not perfect as seen in the corresponding symmetric system discussed in the previous sections.

4.4.3 Detection of Foreign Ligands: Final Discussion

In this section, several interesting results were obtained concerning the detection of foreign ligands task. These findings can be briefly summarized as:

- Educated populations of detectors perform significantly better detection than random populations. However, around 33% of the invaders escape detection when only one educated population of detectors ensures detection. This value increases to 98% when a random population is considered;
- The anergy mechanism globally reduces the frequency of long interactions between presenters and detectors. This reduction is higher for a bigger number of populations in the repertoire;
- Extended repertoires of detectors ensure perfect self/nonself discrimination, when costimulation is used to signal detection of foreign ligands;
- Repertoires generated after extensive education processes have a higher decrease in frustration for the presenter that displays the foreign ligand, consequently, higher detection ratios;
- There is an optimal in the performance of the detection system which is obtained in 3 and 4-cluster systems;
- If restricted connectivity is considered, perfect self/nonself discrimination is independent of the number of agents in the system;
- Both the positive and the negative education process are crucial to achieve perfect discrimination self/nonself.

The education process ensures that for an arbitrary presentation of ligands, the set of selected detectors will perform interactions with maximal affinity but in a frustrated dynamics. When the invader is introduced in the system, each detector has its ligand in a random position of the IList, because the invader's ligand has

not shaped ILists in the education process. Consequently, there is an arbitrary number of detectors that have maximal affinity for the ligand of the invader and, additionally, the invader high affinity for these detectors. Thus, the affinity of this interaction is maximal in both directions and none of the remaining agents is capable of destabilizing this interaction.

This frustration reduction is amplified by anergy, due to the fact that the probability of the invader's ligand being in the top position of the detectors' IList increases with the increase of the number of ILists available in the extended repertoire of detectors. The change in the "normal" profile of the interactions of the presenter that displays the foreign ligand is signaled through the costimulation process and the invader is detected.

To summarize, this section demonstrates that perfect self/nonself discrimination is possible in CFSs. These results suggest that CFSs can be seen as a valuable option for intrusion detection systems (IDS) in complex systems. In addition, these results can also provide insights to more deeply understand the functioning of the immunological mechanisms from a completely different perspective.

4.5 Detection of Abnormal Self Presentations: Abnormal Growth of Self Ligands

The previous sections show that CFSs respond to ligands, which had never been presented during the education stage. Returning to the example of proofreading a text, the detection of a foreign ligand corresponds to finding a foreign word which does not belong to the idiom in which the text was written. As stated before, this kind of detection is important, but it is easily accomplished with algorithms based on a database, in which all words of a given idiom are listed. Hence, this type of detection by itself may not be so interesting from a computational point of view. If the anomaly detection system can join the ability of detect other kinds of perturbations, extra value to the anomaly detection system could be added. Thus, different types of anomalies will be investigated in this and in the next sections concerning anomalies that comprise perturbations on the number of ligands presented and that belong to the system - homeostatic perturbations.

In order to better understand what kind of studies will be performed concerning the detection of changes in the frequency of self ligands, the example of proofreading a text will be used as example. Figure 4.43 illustrates the type of perturbation that will be investigated, using as example the 2^{nd} article of the The Universal Declaration of Human Rights.

Article 2.
Everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind, such as race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status.

Article 2.
Everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind, such as race, as colour, as sex, as language, as religion, as political or other opinion, national or social origin, property, birth or other status.

Figure 4.43: Detection of abnormal presentations concerning changes in presentation frequency: original and perturbed text, at the top and at the bottom, respectively.

The original and the abnormal text differ only on the number of "as", which means that the frequency of its appearance increased in the perturbed text. However, the word belongs to the idiom and it appeared in the normal text. Returning to CFSs, if the same happens in a complex system as when, suddenly, an arbitrary sequence starts appearing more often than usually did in the education and calibration stages, the computational system presented an increase in the ligand coding

that sequence. Due to the fact that the system works with a constant number of agents, the increase in frequency of a given ligand implies the disappearance of others in the presentation.

The capacity of detecting changes in the presentation frequency coding normal behavior is crucial in an anomaly detection system. In this sense, the anomaly detection system should detect both perturbations due to foreign information, and perturbations caused by a change in the frequency of presented ligands.

How detecting changes in the frequency of appearance of educated ligands can be accomplished will be discussed in the light of CFSs framework next.

4.5.1 Simulation and Parameters

In order to investigate the capacity of CFSs to detect changes in the frequency of the ligands presented, a 3-cluster system of 60 agents of each type, equally divided was considered. The repertoire of 40 populations of detectors was educated with τ_{ed}=150 to ensure the surveillance of the system. As in the previous section, the ratio was calculated at τ_1=0.15×τ_{ed}, τ_2=0.3×τ_{ed} and τ_3=0.6×τ_{ed}. The separation time of the interactions is τ_{sep}= 1.5×τ_{ed}, after which the interaction is stopped and the detector changed through the anergy process, τ_{an}=2.

The change in frequency was simulated by the sequential repetition of the ligands of the first column of ligands in the next ones. In order to better understand the changes made in the different stages, the presentation used in the education and in the calibration stage versus one of the presentations used in the detection stage is shown in Figure 4.44. In the detection stage the ligands placed in columns 2 and 3 were replaced by the ligands of column 1, which were pointed out in red. The repetition of ligands was made by cluster which means that there are no changes concerning the cluster in which the repeated ligands were displayed.

For each perturbation, 100 systems were used in the calibration and in the monitoring phase without and with perturbation, during 10^4 iterations each. The values of $f^{o}_{i,>\tau}$ per presenter were determined in the calibration stage, which corresponds to the maximal value of $f^{S}_{i,>\tau}$ in an arbitrary system, in a given τ of analysis. After the calibration phase, the response in the absence of perturbation is tested, to determine the response in this case. Finally, different perturbations were introduced in presentations to investigate the capacity of detecting changes in the frequency of presentation of the ligands. Sequentially, the ligands in 1, 2, 4, 6 and 8 columns were

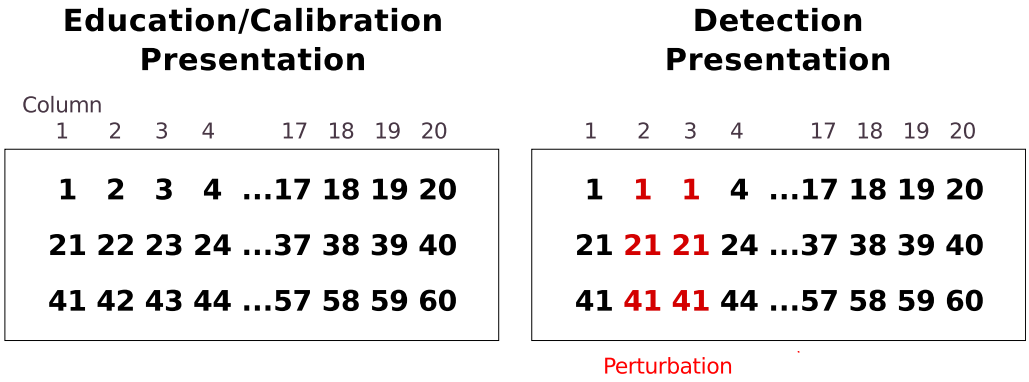


Figure 4.44: Presentations used during the education and calibration stages (Left) and during the detection stage (Right).

replaced by the ligands presented in column 1, which corresponds to a perturbation of 5%, 10%, 20%, 30% and 40%, respectively.

In order to better understand the presentations in each stage, the histogram of the ligands displayed in calibration and in 2 different detection stages are shown (Figure 4.45, A, B and C, respectively). During the calibration stage all ligands were displayed with equal frequency - each ligand appears 100 times, each presenter displays one of the ligands in each simulated system (Figure 4.45A). This presentation was the same of the education stage. To illustrate the detection stage two different perturbations were selected. In the first case, the ligands of column 2 - 2, 22, 42 - were replaced by the ligands of column 1 - 1, 11 and 41 -, which corresponds to a perturbation of 5% in the columns. Thus, the last ones have the double of the occurrences when compared with the remaining ones, while the first ones are absent (Figure 4.45B, Perturbation 5%). In the biggest perturbation imposed, 40% of the columns were changed, which means that ligands 2, 3, 4, 5, 6, 7, 8, 9, ligands 22, 23, 24, 25, 26, 27, 28, 29, and, finally, ligands 42, 43, 44, 45, 46, 47, 48, 49 were replaced by ligands 1, 21 and 41, respectively. Thus, ligands 1, 21 and 41 register 900 occurrences while the remaining ligands were presented once in each perturbed presentation, so each has 100 occurrences, one per system (Figure 4.45C, Perturbation 40%).

For each system simulated the number of presenters that respond to the perturbation is quantified according with the ratio, $\mathcal{R} \geq 1$, with F=1.2. Responses to the perturbations were analyzed for different connecivities: total and limited connectivity were considered, $k = 60$, $k = 30$ and $k = 15$, respectively. The parameters considered are presented in the table below (Table 4.3).

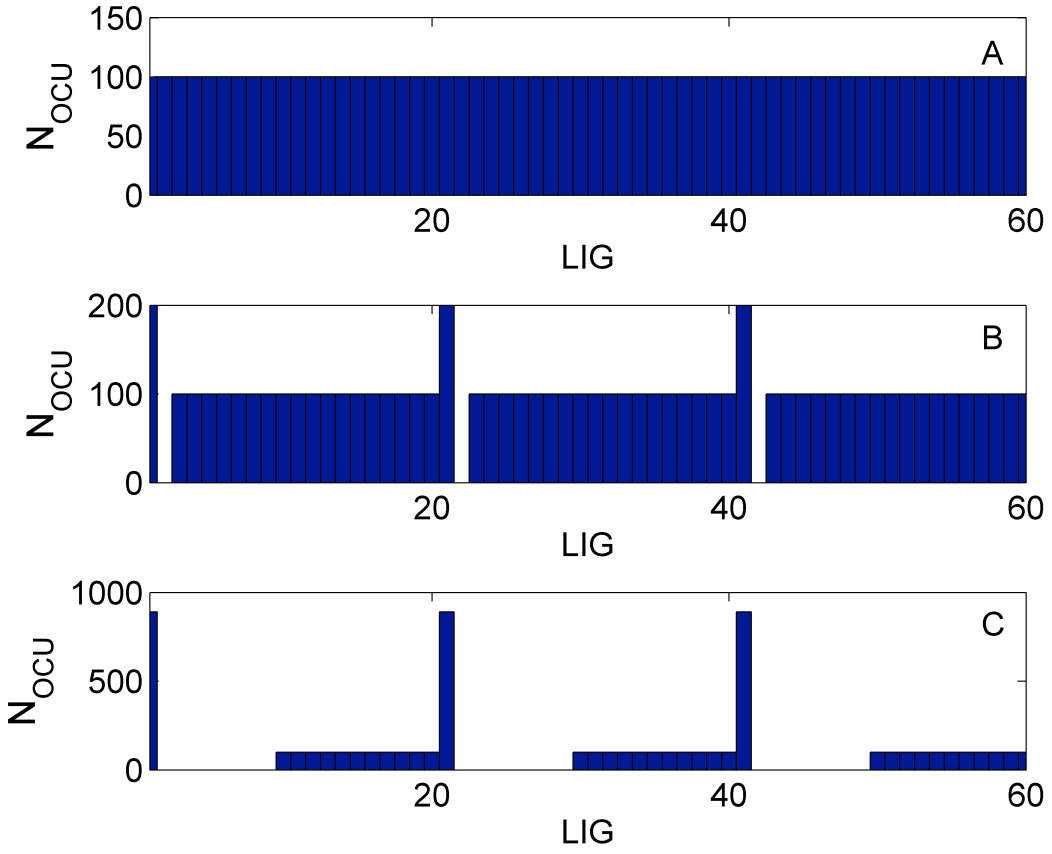


Figure 4.45: Histograms representing the number of times each ligand was presented. (A) Histograms obtained for the calibration state. (B, C) Histograms obtained after the monitoring stage with abnormal presentation - perturbation of 5% and 40%, respectively.

Table 4.3: Parameters considered in simulations of the responses against abnormal frequencies.

k	τ_{ed}	τ_1	τ_2	τ_3	τ_{sep}
15	73	11	22	44	110
30	87	13	26	53	131
60	150	23	45	90	225

4.5.2 Numerical Results

4.5.2.1 CFSs detect abnormal growth of agents

To analyze the effect of the perturbations introduced on frustration, the number of presenters that decreased their frustration relatively to the calibration stage - the number of presenters that have $\mathcal{R} \geq 1$, $n_{\mathcal{R}\geq 1}$, is calculated and it is represented for each simulated system, S, according to the perturbation imposed in τ_1 (Figure 4.46). In order to compare the responses in the remaining lifetimes analyzed, the average number of presenters, which have $\mathcal{R} \geq 1$, $\overline{n_{\mathcal{R}\geq 1}}$ are listed (Table 4.4).

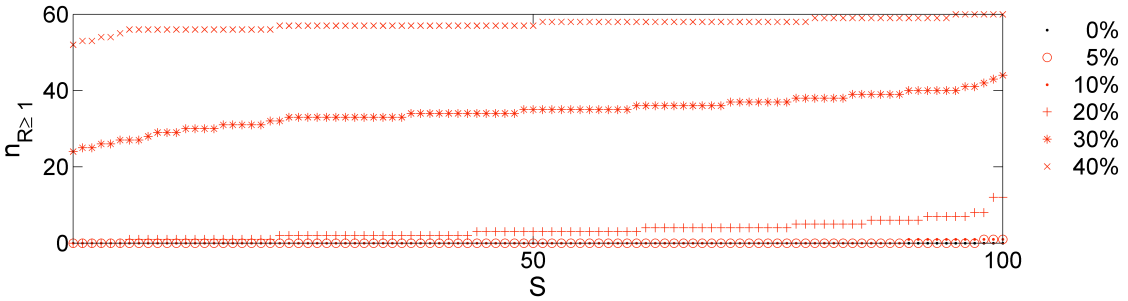


Figure 4.46: Number of presenters with $\mathcal{R} \geq 1$, $n_{\mathcal{R}\geq 1}$, as function of the perturbation imposed with the system simulated, S.

Table 4.4: $\overline{n_{\mathcal{R}\geq 1}}$±std for all systems and lifetimes simulated.

Perturbation (%)	τ_1	τ_2	τ_3
0	0±0	0.05±0.2	0.25±0.5
5	0.03±0.2	0.13±0.4	0.49±0.7
10	0.11±0.3	0.83±0.9	0.95±1.0
20	3.27±2.3	8.14±3.2	6.43±2.2
30	34.50±4.1	37.97±2.9	30.58±3.5
40	57.40±1.5	55.44±2.0	53.20±2.3

It is interesting to notice that the system tolerates smaller perturbations. There is almost no response when 1 or 2 columns are replaced by ligands of the column 1. This changes considerably with the increase of the perturbation. When 6 columns are copied - perturbation of 30% - , more than 50% of the presenters have a less frustrated dynamics, and in case 8 columns are copied - perturbation of 40% - almost all the presenters register a decrease in frustration in their dynamics.

Another interesting result is that the extended repertoire of detectors and the anergy mechanism is crucial to perform detection of self perturbations in the frequency of the educated ligands, as well as the costimulation. As in the detection of foreign ligands, in the absence of anergy, the detection is poorer, as shown in Figure 4.47.

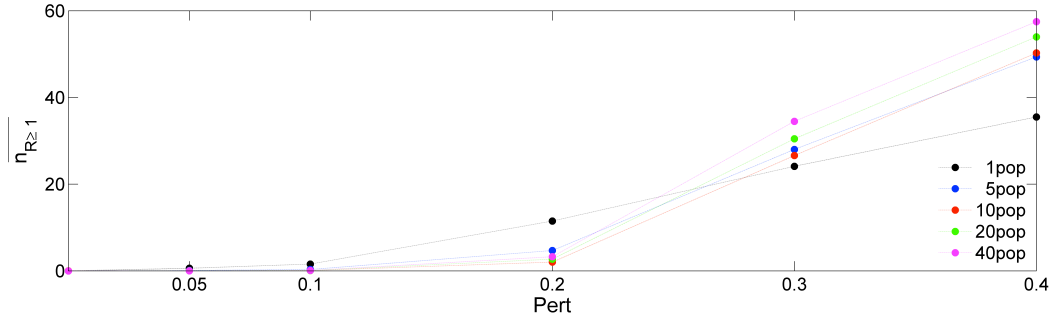


Figure 4.47: Average Number of Presenters with $\mathcal{R} \geq 1$, $\overline{n_{\mathcal{R}\geq 1}}$, as a function of the system simulated, S, and according to perturbation.

The number of presenters that have $\mathcal{R} \geq 1$ in each case increases, in general, with the number of populations considered in the repertoire of detection.

These results indicate that responses to homeostatic perturbations in frequency are possible in CFSs. Similarly to the results obtained in the detection of non self ligands, restricted connectivity can also improve, responses to the abnormal expression of ligands. The performance of the anomaly detection system in the case of restrict connectivity is the subject of the next section.

4.5.2.2 Amplification of responses with limited connectivity

The results obtained with total connectivity show that there is a global decrease in the frustration of the system, proportional to the size of the perturbation imposed.

In order to increase the responses for even smaller perturbations, the connectivity of detectors was reduced to k=30 and k=15. All the systems were simulated again. The same plot concerning the number of presenters that have $\mathcal{R} \geq 1$ is presented for limited connectivity (Figure 4.48).

The reduction of the connectivity increases the number of presenters that decrease their frustration for each perturbation. The lower the connectivity considered, the stronger the response to the perturbation. In the case of k=15, even the repetition of a single column starts to be noticed with the decrease of the frustration of a macroscopic number of presenters.

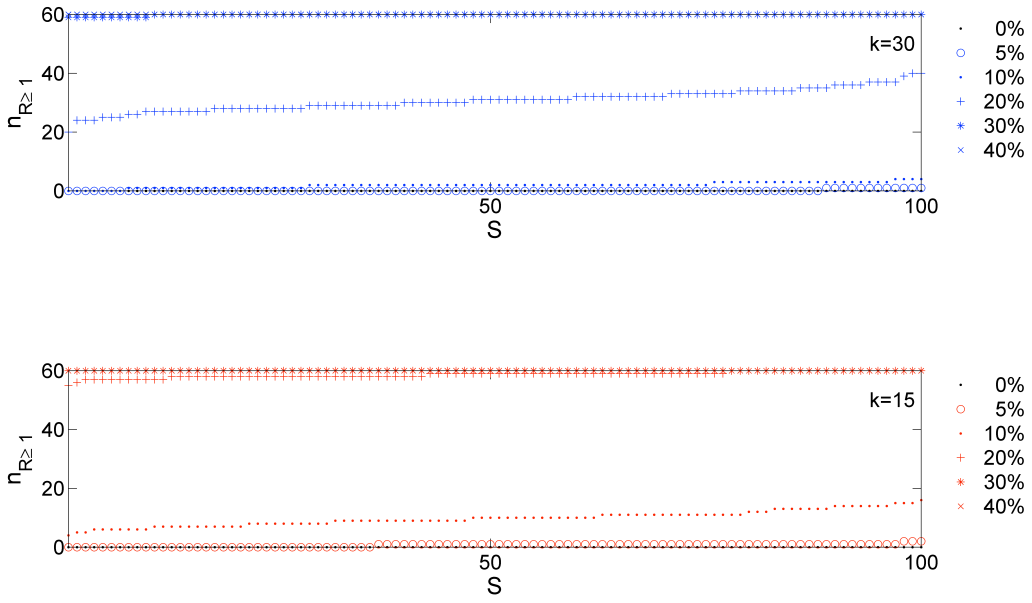


Figure 4.48: Number of presenters with $\mathcal{R} \geq 1$, $n_{\mathcal{R}\geq 1}$ as function of the system simulated and according with the perturbation and the connectivity considered.

Also, the magnitude of the responses increases with the reduction of the connectivity considered in the system. A typical dynamics of a system in the calibration and in the monitoring stage is presented in Figure 4.49 for 2 different perturbations - 5% and 40% - and for different connectivities - k=60, k=30 and k=15.

It is important to point out that the results presented in Figure 4.49 for both cases represent typical results. Other 99 systems were considered, from which the average of the number of presenters having $\mathcal{R} \geq 1$, $\overline{n_{\mathcal{R}\geq 1}}$, was calculated and represented as function of the perturbation for each perturbation (Figure 4.50). For these results ratios were calculated at $\tau = \tau_1$.

For k=15, only a column change causes a decrease in frustration, which increases with the increase of the number of repeated columns. Repeating 4 columns, all the 60 presenters have $\mathcal{R} \geq 1$. For the double of connectivity, k=30, the responses start with more than 1 column changed, while the decrease of the frustration of all the presenters is accomplished for more than 4 columns changed. If none of the columns is changed, none of the presenters has $\mathcal{R} \geq 1$, independently of the connectivity considered, as expected and also consistently with the choice of F.

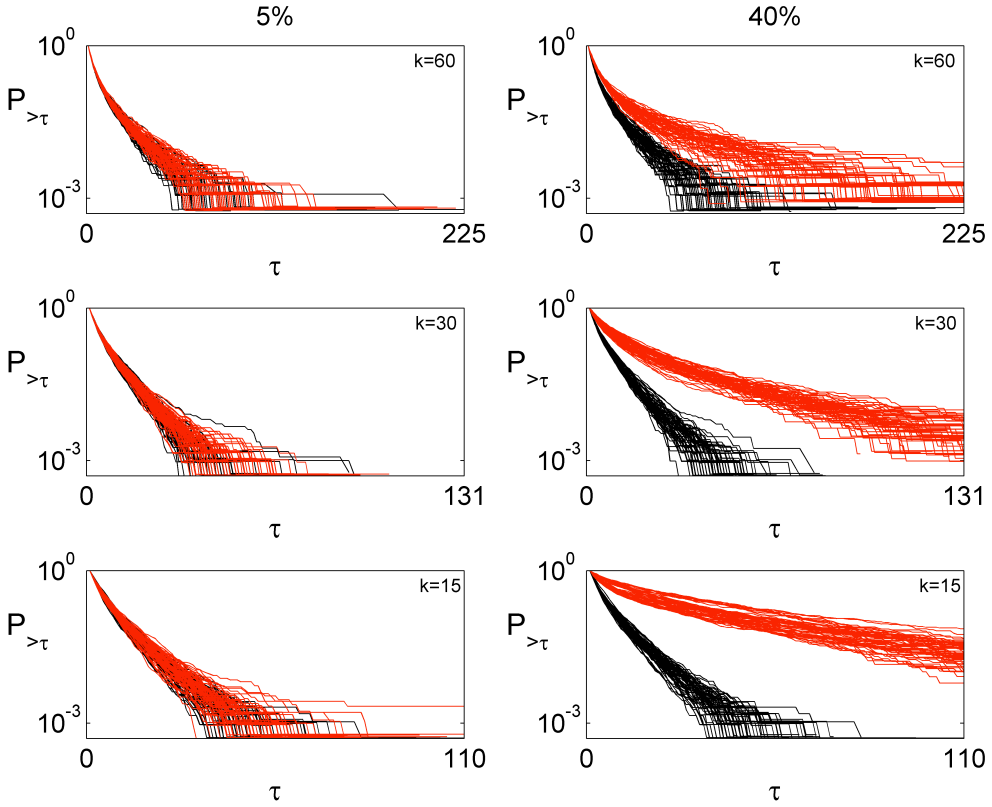


Figure 4.49: Probability that each presenter establishes a conjugation longer than τ iterations, $P_{>\tau}$, as a function of τ, depending on the perturbation and the connectivity considered. Black: Histograms obtained during the calibration phase. Red: Histograms obtained during the monitoring stage with perturbation. Two different perturbations (5% and 40%) and 3 different connectivities were considered. In these results τ_{sep} was set equal to 225, 131 and 110, respectively.

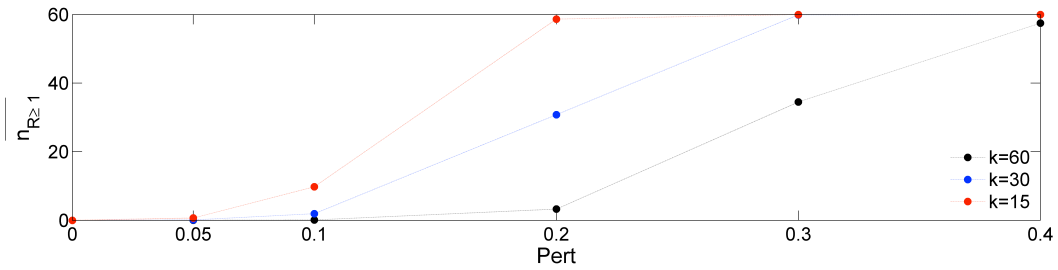


Figure 4.50: Average of the number of presenters having $\mathcal{R} \geq 1$, $\overline{n_{\mathcal{R}\geq 1}}$, as a function of the perturbation imposed, Pert, for different connectivities.

4.5.3 Abnormal Growth of Self Ligands: Final Discussion

In the previous section it was shown that CFSs are capable of performing perfect self/nonself discrimination if an extended repertoire of educated detectors ensures detection and, additionally, if anergy and costimulation are considered. This was an interesting result especially from an immunological point of view. However, from a computational point of view, other approaches can equally well perform discrimination self/nonself with more or less difficulty.

More interesting than having a method that ensures perfect self/nonself discrimination is having a method that combines perfect self/nonself discrimination with the detection of homeostatic perturbations, for example due to changes in the frequency of presentation of the ligands. Along this section, it was shown that CFSs simultaneously produce both types of detections. Briefly, the main findings of this section were:

- CFSs are capable of detecting changes in frequency for perturbations above a given value - for instance 20% of ligands changed in the system - if an extended repertoire of detectors is considered with anergy. Perturbations below this value are tolerated as normal;

- Lower connectivities increase the response to abnormal presentations, both in the number of presenters that deliver activation signals and in the amount of the signal delivered.

Based on an analysis of detectors ILists, it is easy to understand why CFSs are capable of detecting these perturbations. The increase in the number of some ligands in the system implies that others are not expressed. There is an increase in the connectivities' list of the number of presenters that display the same ligand. Consequently, interactions leading to changes of conjugations are less frequent because the probability that a detector encounter two presenters with the same ligand increases. Every time this happens, the possibility of optimization fails and, consequently, the stability of the interactions increases.

The capacity of detecting homeostatic perturbations, due to changes in the frequency of presentation of some ligands is not a surprising result: despite the fact that the system is different, frustrated systems presented in [20] already suggested that this type of detection would be possible. However, this is not the only type of homeostatic perturbation that can be defined in a CFS. The detection of homeo-

static perturbations not related with frequencies of ligands presentations will be the issue of the next section.

4.6 Detection of Abnormal Self Presentations: Presentations with Different Sets of Self Ligands

Presenters can display different configurations of self ligands. Some configurations are not presented during the education process and hence their occurrence during the monitoring phase can provide information concerning a deviation from normality. Abnormal presentations thus correspond to the presentation of a never seen combination of self ligands. In the examples explored in this section, all ligands are presented during the education process with the same frequencies, and it is imposed that some ligands are never presented together. It is the purpose of this section to show that cellular frustrated systems can also detect perturbations of this kind. These perturbations are denominated by abnormal self detections or detect of abnormal self presentations.

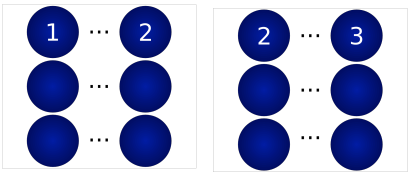
To understand the relevance of detecting this type of perturbations consider again the example of proofreading a text. Abnormal self detection corresponds to the ability of detecting sequences of words written in an improper order, as when if words are reshuffled in a text. In those cases, all words are self, but their ordering spoils the meaning in the sentence.

In cellular frustrated systems abnormal presentations occur when presenters display ligands that have never been presented together during the education process. Consider the possible presentations of two different presenters. In the example in Figure 4.51, presenters display 2 different ligands from 4 available ones. One agent presents ligand L_1 and the other ligand L_2. Four different configurations are presented during repertoire education and defined in the Table in Figure 4.51A. For instance, the first agent could present L_1=1 while the second presents L_2=2, during the first configuration. An abnormal configuration in this example would correspond to the simultaneous presentation of L_1=1 by the first presenter and L_2=3 by the second (Figure 4.51B).

Abnormal self detection requires detecting abnormality even when all ligands are presented during repertoire education and all ligands are presented with the same frequency. The motivation of this section is to discuss whether anomaly detection can be context dependent. This will be the issue of this section.

A

Presentation 1 Presentation 2



Self Presentations

Presentation	L_1	L_2
1	1	2
2	2	3
3	3	4
4	4	1

B

Abnormal Presentations

Presentation	L_1	L_2
1	1	3
2	2	4

Figure 4.51: Representation of self and abnormal self presentations. A) Two different presenters display 2 different ligands from 4 available ones. Four different configurations are presented during repertoire education, as listed in the table of Self Presentations. B) Abnormal presentations would correspond to the presentation of L_1=1 by the first presenter and L_2=3 by the second, or L_1=2 by the first presenter and L_2=4 by the second, as listed in the table on the right.

4.6.1 Simulations and Parameters

In order to investigate the capacity of detecting abnormal presentations, a 3-cluster system with 60 agents per type was considered. For the study of abnormal presentations, it is necessary to present at least two different presentations in the education phase. Here, two presentations of ligands were presented in alternance having half of the ligands in common. Presentations can be divided in three blocks of ligands: one fixed block (block 2) that is always present and two blocks alternating (blocks 1 and 3) in regular windows of presentation - lasting 5000 iterations (Figure 4.52). Presentation 1 corresponds to the presentation of the combination of blocks 1 and 2 and presentation 2 to the presentation of blocks 2 and 3. These presentations could be accomplished when each presenter displays only two different ligands. For example, presenter number one could show ligands 1 and 11, during presentations 1 and 2, respectively. All ligands were displayed independently of the stage by the same presenter.

During the education stage, 40 educated populations were selected with three different connectivities: total connectivity (k=90) and limited connectivity (k=30 and k=15). It is assumed that τ_{ed} is the maximal conjugation lifetime registered for the first population after the $1x10^7$ iterations.

After the education process, the calibration stage is performed. This involves presenting a set of configurations, $\mathcal{C}_S$, representative of the configurations presented during the education stage - in this case only 2 different configurations are considered (Figure 4.53)- and calculating the frequency of conjugations lasting longer than τ for each presentation j, $f^j_{i,>\tau}$. The maximum frequency of conjugations lasting longer

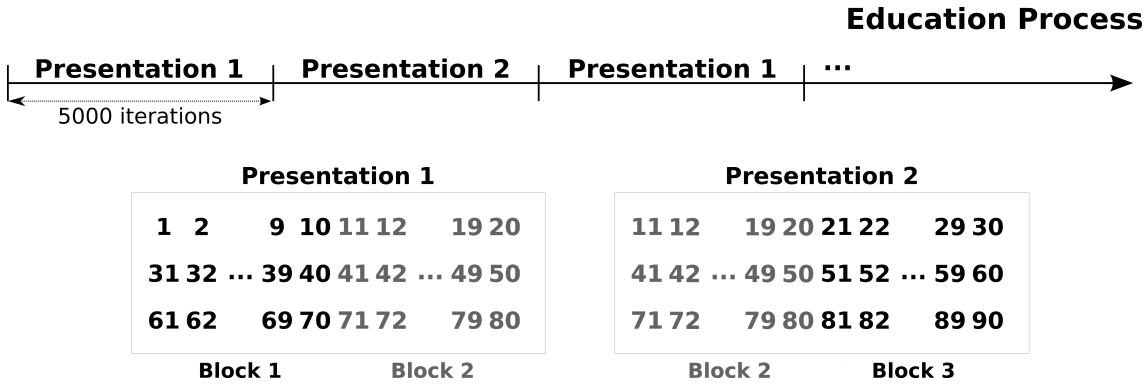


Figure 4.52: Alternative presentations displayed by presenters in the education process. Top: during repertoire education configurations 1 and 2 are sequentially presented for 5000 iterations. Bottom: all ligands presented in the two configurations are different. A sub-set of ligands is present in both configurations (Block 2), while the remaining ligands are specific to each configuration.

than τ for the ensemble of presentations can then be defined by:

$$f^{o}_{i,>\tau} = max_j\{f^{j}_{i,>\tau}\} \tag{4.5}$$

where the j index runs over the set of representative configurations.

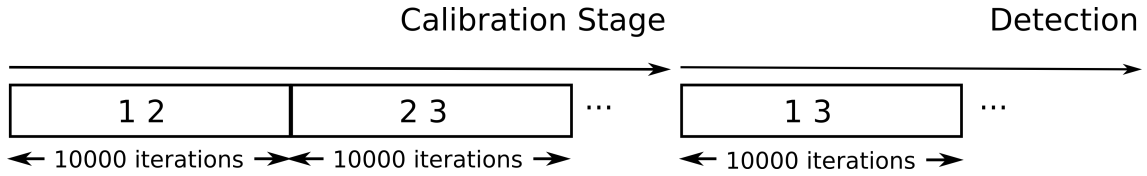


Figure 4.53: Alternative presentations displayed by presenters in the calibration and monitoring phase. Only 2 different configurations are considered - Presentation 1 and Presentation 2. The abnormal presentation illustrated testes a configuration corresponding to a mixture of the presentations 1 and 2 in different proportions.

Using these generalized definitions for the calibration frequencies $f^{o}_{i,>\tau}$, detection ratios are defined as before, in section 2.3.1. Furthermore, the number of presenters responding to a perturbation - i.e., having $\mathcal{R} \geq 1$ will also be determined as in the previous section. The abnormal presentations tested mix presentations 1 and 2 in different proportions as shown in Figure 4.54. In practice, successive columns of block 1 were replaced by equivalent columns of block 2, until only one column of block 1 is presented.

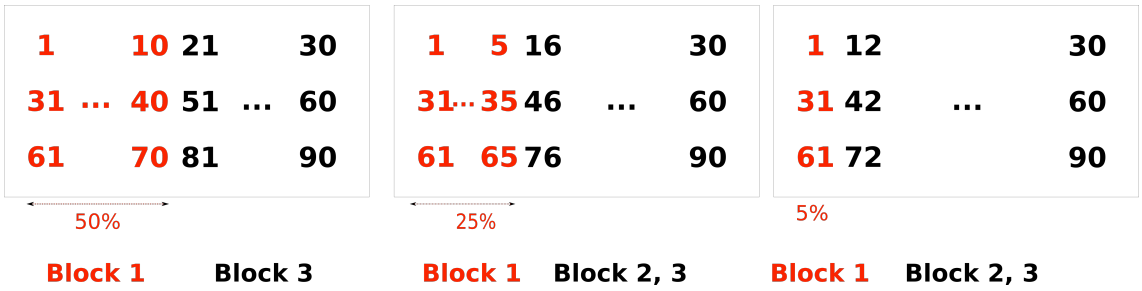


Figure 4.54: Example of perturbations imposed to the system. Successive columns of ligands corresponding to block 1 were replaced by equivalent columns of ligands from block 2, until only one column of ligands from block 1 is presented - ligands from block 1 were replaced by ligands from block 2.

4.6.2 Numerical Results

4.6.2.1 Anergy ensures robust collective responses

The first study concerning abnormal presentations tested the impact of the anergy on the response of one particular agent to the perturbation. In the absence of anergy a presenter may or may not respond, even if other agents respond in the population. In the example in Figure 4.55, the dynamics of a presenter was analyzed for the 100 simulations run during calibration (CAL) and monitoring stages, without and with the perturbation (MWP and MP, respectively). When no anergy is considered, the population of presenters and detectors is always the same. However, the dynamics of the presenter agent varies somewhat considerably. For instance, it can establish a negligible number of long conjugations or a much more considerable number. Results can also vary considerably depending on the set of detectors present in the population, as can be appreciated from the difference on the histograms presented in figure 4.55 A and B.

Responses to abnormal perturbations are also very different. In one case the presenter responds vigorously (Figure 4.55 B) or it does not respond (Figure 4.55A). However, it should be noted that in both cases there are agents responding in the population.

The introduction of anergy averages responses over the different combinations of detectors. As a result, responses become less intense but more constant for all presenters that will ever respond (Figure 4.55C). In this sense, one can argue that anergy renders the response of the population more homogeneous and less confined to a sub-set of presenters. In other words, with anergy abnormal self detection becomes a collective phenomenon.

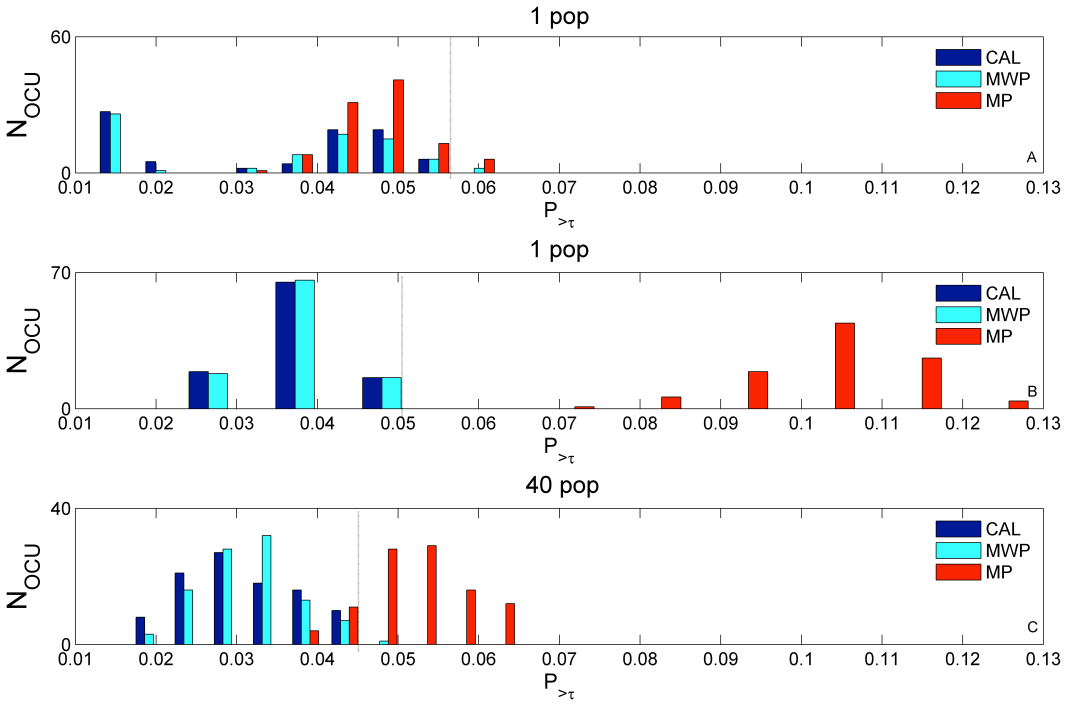


Figure 4.55: Histogram of $P_{>\tau}$ for the same presenter and different repertoires. Two repertoires with 1 population are represented in (A) and (B), while a repertoire with 40 populations and anergy is presented in (C). The dynamics of a presenter was analyzed after 100 simulations run during the calibration (CAL) and monitoring stages, without and with the perturbation (MWP and MP, respectively).

These results can be even better for small connectivities. The study of the effect of limited connectivity on detection will be discussed in the next section.

4.6.2.2 Limited connectivity promotes better responses

Limited connectivity promotes better education in large systems without prejudice of foreign ligands detection. In this section, the effect of limited connectivity on the detection of abnormal self presentations is analyzed. In order to do that, the connectivity of each detector was reduced to 30 or 15 ligands and several perturbations were imposed on the system. All simulations were performed with a repertoire of 40 populations. The average number of presenters with $\mathcal{R} \geq 1$, $\overline{n_{\mathcal{R}\geq 1}}$, as a function of the size of the perturbation imposed and for several connectivities is presented in (Figure 4.56), for a presentation mixing configurations 1 and 2.

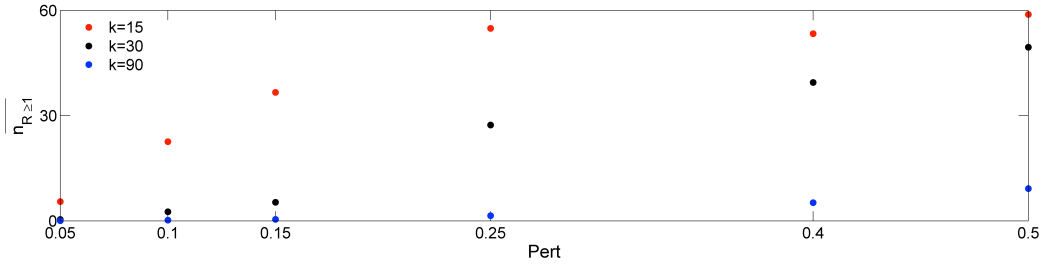


Figure 4.56: The average number of presenters with $\mathcal{R} \geq 1$, $\overline{n_{\mathcal{R}\geq 1}}$, as function of the size of the perturbation and for different connectivities, registered at τ_1. The perturbation corresponds to the replacement of columns of ligands, represented in Figure 4.54, from one configuration into the other. When the size of the perturbation equals 0.05, 5% of the ligands were replaced, corresponding to the replacement of a single column. The other perturbations considered involved changing 10%, 15%, 25%, 40% and 50% of the ligands.

If 50% of the columns of the second presentation are replaced by columns of the first, a massive response involving 59.0±1 agents is mounted - within the 60 presenters available. The number of activations decreases to 54.9±1 or 5.5±2 when the perturbation decreases to 25% or 5%, respectively. All perturbations imposed were detected for k=15, with none of the presenters activated in the absence of perturbation.

In order to see the impact of perturbations on the dynamics, histograms of conjugation lifetimes for populations with 50%, 25% and 5% of the columns changed are shown in Figure 4.57 A, B and C, respectively. Red lines correspond to the perturbed system, while the black are relative to the presentation without perturbation.

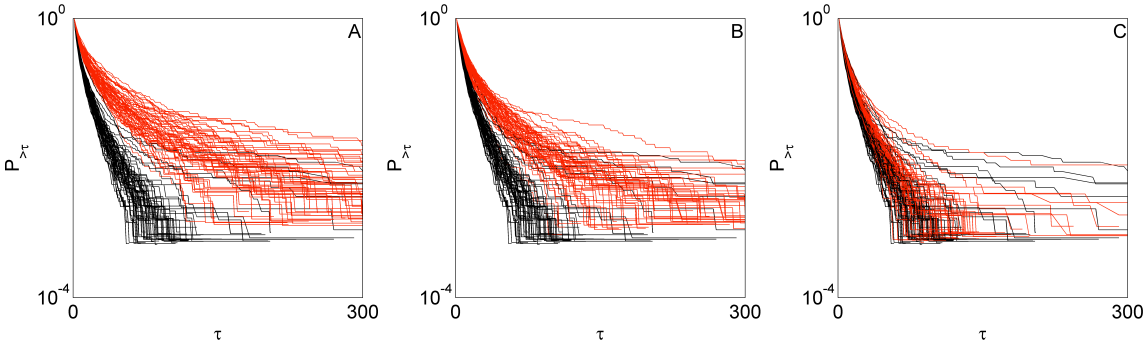


Figure 4.57: Histograms demonstrating the response to perturbations when populations have 50%, 25% and 5% of the columns changed (A, B and C). Here the connectivity is k=15. Red lines correspond to the perturbed system, while black lines are relative to a presentation without perturbation.

The system responds to all abnormal perturbations when the connectivity is k=15. At the same time it is tolerant when the educated presentations are displayed. Tolerance is not perfect in this case as can be concluded from the results obtained in the absence of perturbation listed in Table 4.5. Eventually one agent can be activated, although this occurs only in 3% of the populations. Tolerance could be reduced by increasing the tolerance F factor, although in that case reactivity would be reduced. Other possible strategies to increase tolerance would be to use a sequence of detection systems. Indeed, these 3% of activations occur in different agents, and hence by considering independent populations their impact should be reduced.

Table 4.5: $\overline{n_{\mathcal{R}\geq 1}}$ in the absence of perturbation.

			τ_1
k	15	30	90
m±std	0.03±0.2	0.03±0.2	0±0

4.6.3 Abnormal Presentations of Different Self Ligands: Final Discussion

In addition of being capable of performing perfect discrimination self/nonself and detecting perturbations due to changes in frequencies of presentation of the self-ligands, CFSs are also capable of detecting abnormal self-presentations. These im-

portant results rely on a number of other interesting features exhibited by these systems and summarized below:

- The education process is capable of educating detectors for 2 independent sets of ligands presented. After the education process, detectors ILists have information concerning correlations among the ligands presented in each configuration.
- During the monitoring stage, detectors can be tolerant relatively any of the two configurations presented. For a repertoire of 40 educated populations, activations are negligible in number, and even if a single activation would take place, it is possible to distinguish this from the activation of a nonself presenting ligand.
- The change of a single column is enough to trigger a response for k=15, which signals the perturbation.
- Stronger responses are obtained for the strongest perturbations imposed and smallest connectivities in the system.

At first sight, it seems that connectivity should be the smallest possible. However, this is not true. Although the limited connectivity ensures stronger responses, it is important to bear in mind that the reduction of connectivity has a double effect. Smaller connectivities increase responses against perturbations, because ILists can be better educated (or ordered) in order to guarantee maximal frustration. Furthermore, small changes in the presentation can have dramatic effects on the dynamics, when the connectivity is limited.

The abnormal self detection discussed in this section rely on the existence of correlations in ILists organization to produce detection. These results can be easily understood with a simple and yet general model, involving only 4 ligands and 2 different presentations. This is illustrated in Figure 4.58, where two different presentations presented during the education stage are represented. In the first configuration an agent from the first cluster presents ligand A, while an agent from the second cluster presents ligand B. On the second configuration these two agents present instead ligands C and D, respectively. As a result, several detectors can have emerged from the education process. Detectors from the first cluster will certainly rank ligand B before ligand A, and ligand D before ligand C. This, however, does not establish what the relative order of ligands A and D and B and C will be. In

fact, all the ILists represented in Figure 4.58A would have maximally frustrate the dynamics of the population during the presentation of configurations 1 and 2.

The abnormal self detection phenomenon appears when the presentation 3 represented in Figure 4.58B is presented during the monitoring stage. When this happens it is clear a detector belonging to the first cluster and having the IList favors interactions with a ligand displayed by a presenter from the first cluster rather than the second. This will necessarily lead to large conjugation times and a reduction in frustration.

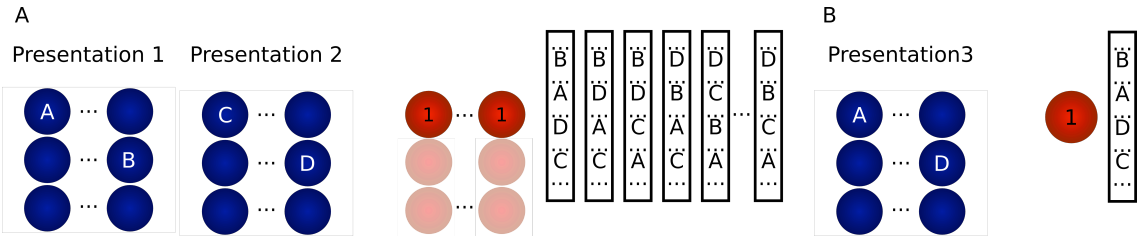


Figure 4.58: Generic representation of a 3-cluster system with abnormal presentation. A) In Presentation 1 an agent from the first cluster presents a ligand A, while an agent from the second cluster presents a ligand B. On the second configuration these two agents present instead ligands C and D, respectively. As a result, several detectors can have emerged from the education process. Detectors from the first cluster will certainly rank ligand B before ligand A, and ligand D before ligand C. This, however, does not establish what the relative order of ligands A and D and B and C will be. B) When Presentation 3 is presented during the monitoring stage, a detector belonging to the first cluster and having the IList shown, favors interactions with a ligand displayed by a presenter from the first cluster rather than the second. This will necessarily lead to a reduction in frustration.

Until now, only one or two presentations were shown in the education process. In both cases, the system learns correlations present in the configurations presented and signals deviations from them. This result allows applications of the algorithm in systems in which one or two presentations are enough to capture the normal behavior of the system under analysis. However, more complex behaviors can require a larger diversity in presentations. Can CFSs capture correlations in a more general class of systems displaying a larger diversity? This is the subject of the next section.

4.7 Detection of Abnormal Self Presentations: Abnormal Presentations of Different Self Ligands and Generalization

4.7.1 Simulation and Parameters

In order to test the capacity of generalization with the increase in the number of the configurations presented, a large set of different presentations was generated and sequentially presented during the education stage. Presentations were built by selecting 60 different ligands - one per agent - within a set of the 126 available ligands in a 3-cluster system. In order to understand what correlations can be learnt in these systems, presentations were controlled. Ligands were distributed into 6 blocks, each one with $126/6 = 21$ ligands, i.e. $21/3 = 7$ possible ligands per block, as presented below:

Table 4.6: Distribution of the ligands per block and cluster.

Cluster	Block 1	Block 2
1	1 2 3 4 5 6 7	8 9 10 11 12 13 14
2	43 44 45 46 47 48 49	50 51 52 53 54 55 56
3	85 86 87 88 89 90 91	92 93 94 95 96 97 98

Cluster	Block 3	Block 4
1	15 16 17 18 19 20 21	22 23 24 25 26 27 28
2	57 58 59 60 61 62 63	64 65 66 67 68 69 70
3	99 100 101 102 103 104 105	106 107 108 109 110 111 112

Cluster	Block 5	Block 6
1	29 30 31 32 33 34 35	36 37 38 39 40 41 42
2	71 72 73 74 75 76 77	78 79 80 81 82 83 84
3	113 114 115 116 117 118 119	120 121 122 123 124 125 126

In each presentation, a random sample of 5 ligands is drawn from the 7 available ligands per block and per cluster. This procedure is repeated for all blocks and clusters. After this selection, ligands are placed in ascending order and displayed by presenters (Figure 4.59). The aim of the ordering is only to reduce the diversity of ligands displayed by each presenter. This diversity in presentation is not a problem

in the education process. Nevertheless, this ordering reduces the variability during the detection (Section 4.7.2.3).

It was assumed that "normal" presentations follow an established sequence of blocks' presentation rule. In this section, "normal" presentations fixed two blocks (blocks 3 and 4) and the remaining alternated (blocks 1 and 2 with blocks 5 and 6), every 2000 iterations. Here, blocks 1 and 2 always appeared together, as well as block 5 and 6. Thus, the two combinations of blocks allowed in the education stage were 1, 2, 3 and 4 and 3, 4, 5 and 6. According to these specifications, more than $2\times(({}^{7}C_{5})^{4})^{3}=10^{15}$ different configurations could be displayed. This number of different configurations is too large and consequently they have never been presented. Hence, agents are required to gain generalization capabilities.

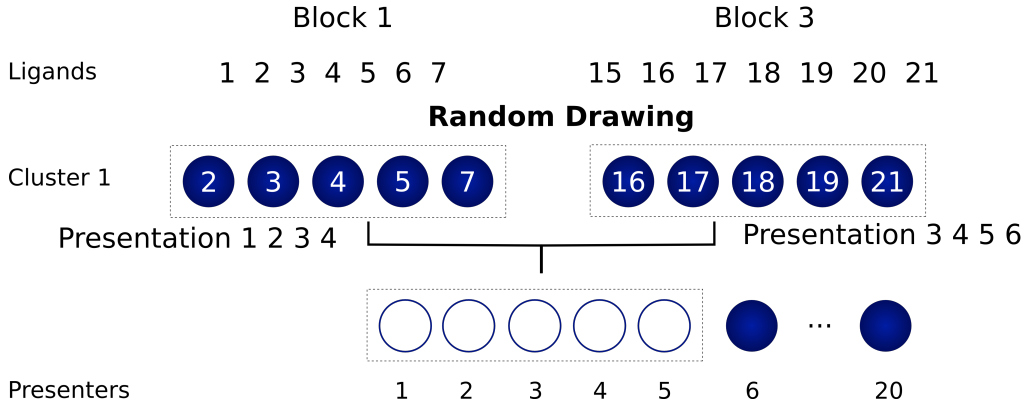


Figure 4.59: Illustration of the random drawing of ligands and their association to presenters, for configurations in which the first five presenters display ligands either of block 1 or block 3. A similar procedure is applied for the remaining presenters.

A repertoire of 40 populations of detectors was educated, considering three different values of connectivity: one in which detectors had maximal connectivity (k=126) and the remaining ones in which detectors had limited connectivity (k=30 and k=15). The τ_{ed} selected for each connectivity was the one achieved in the first registered population after $1x10^{7}$ iterations.

After the education process, 3 different stages were performed: calibration and monitoring without and with perturbation. In the first two stages, the presentation followed the rules established for the education, while in the monitoring phase with perturbation abnormal combinations of blocks were displayed. The abnormal presentation are consisted of combinations that do not follow the rule used in the education process presenting for example blocks 1, 2, 5, 6. Figure 4.60 shows the profiles of presentations of the ligands in the calibration and the monitoring stage

without and with perturbation. Ligands that belong to blocks 3 and 4 appear two times more frequently then the remaining ligands, in the first two stages. However, during the detection, they are absent.

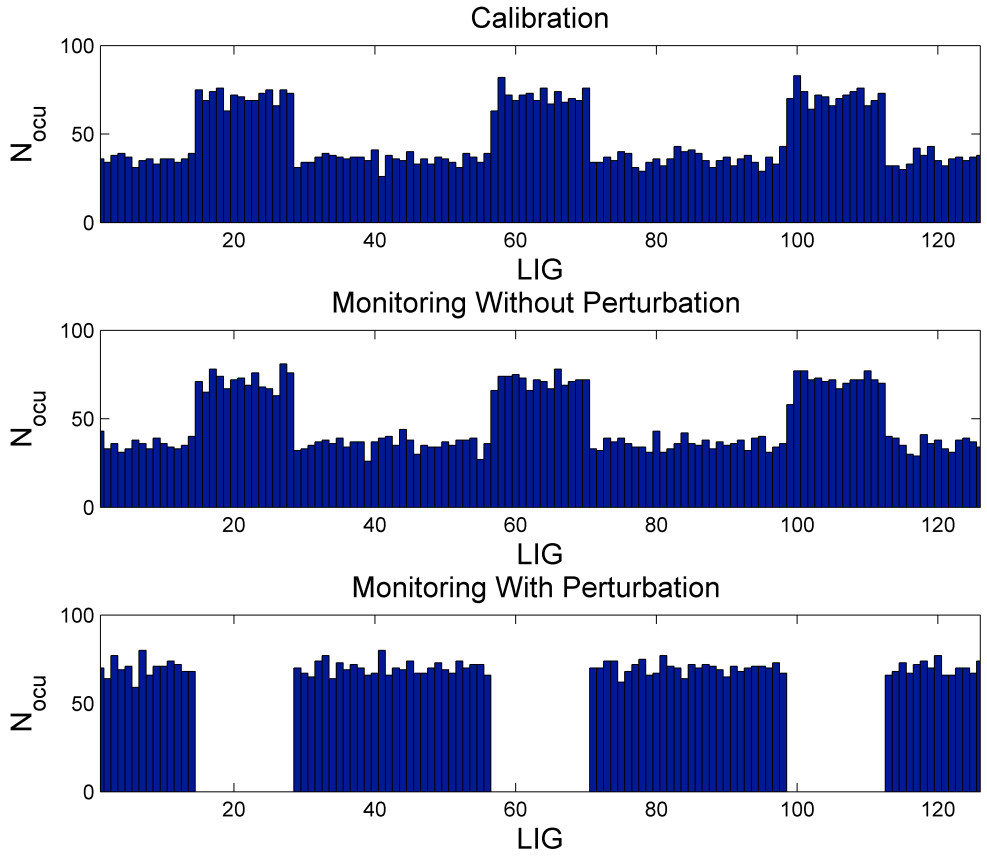


Figure 4.60: Number of presentations for each ligand, presented during the calibration and monitoring stages without and with perturbation. Ligands that belong to blocks 3 and 4 appear two times more frequently then the remaining ligands, in the Calibration and monitoring stage without perturbation. During the monitoring stage with perturbation, ligands belonging to blocks 3 and 4 are absent.

In the calibration stage the activation value ($f^{o}_{i,>\tau}$) was defined as in section 4.5.1 per presenter while in the monitoring stage without perturbation, the response against educated presentations was tested. After this, perturbations were introduced in the presentation.

In each of these stages, 100 systems were simulated during 5000 iterations. Detection responses were triggered when $\mathcal{R} \geq 1$, F=1.2 and using τ_{an}= 2. As in the previous section, the activations were analyzed at three different lifetimes, corre-

sponding to 15% , 30% and 60% of the τ_{ed} - τ_1, τ_2, τ_3, respectively. The discussion concerning the capacity of generalizing and detecting abnormal presentations will be the subject of this section.

4.7.2 Numerical Results

4.7.2.1 CF Systems are able to generalize "normal" behavior

Before studing responses against abnormal presentations, it is crucial to determine how tolerance can be maintained for populations displaying a large diversity on the ligands presented, in the absence of perturbation. As important as the activation of presenters in abnormal presentations is to ensure tolerance in the absence of perturbation. In order to quantify the response in this case, the simulation was run with sequential presentations of blocks shown - blocks 1, 2, 3, 4 and 3, 4, 5, 6 - during the education process. For each simulation, the number of presenters, $n_{\mathcal{R}\geq 1}$, that deliver activation signals as well as the sum of the deviations, D, concerning $f^{o}_{i,>\tau}$, for each presenter were calculated and represented in descending order of their value (Figure 4.61).

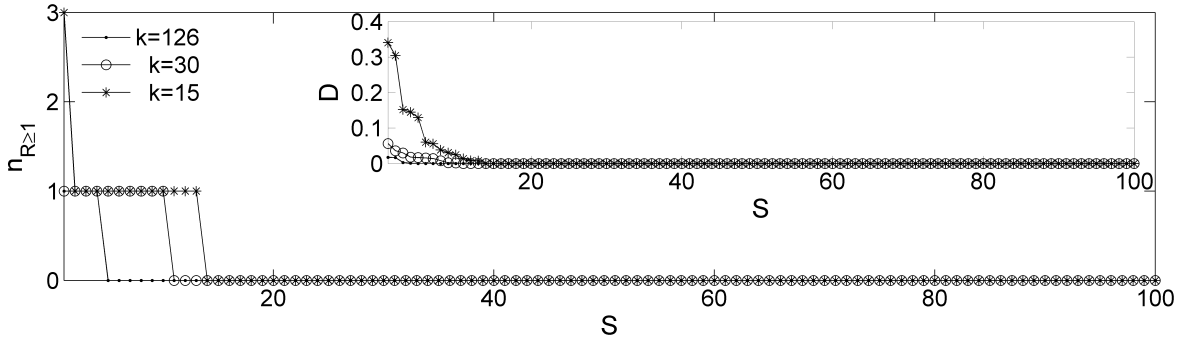


Figure 4.61: Number of presenters with $\mathcal{R} \geq 1$, $n_{\mathcal{R}\geq 1}$, and the corresponding sum of deviations from $f^{o}_{i,>\tau}$, D, in each system S, for different connectivities.

The repertoire of detectors should recognize as "normal" presentations shown in the monitoring phase, which are equivalent to those displayed in the education process. As seen in Figure 4.61, in most of the systems none of the presenters is activated. When activations are triggered, only a single presenter is activated within the 60 possible ones. The only exception occurs with the activation of 3 presenters in a system with k=15, out of the 100 simulated.

The activation of presenters depends on the connectivity of detectors: small

connectivities originate very reactive systems and have stronger responses. Here and due to the fact that only one presenter was activated, the D sum corresponds to the response of that activated presenter. In the triple activation, the sum does not correspond to the first point as it might seem, but to the 7^{th} point (Figure 4.61), which means that the response of the three presenters is only 0.055/3≈0.02, per presenter, a little above the activation $f^{o}_{i,>\tau}$.

This confirms the results obtained in the previous sections - in systems with smaller connectivities detectors capture more detailed correlations among the ligands with which they interact. Hence, small changes in presentation, even in "normal" presentations, can have an effect on the dynamics and can be enough to trigger activations.

Educated detectors develop tolerance towards "normal" presentations. This might seen an obvious result. However, it is important to notice that only a fraction of the universe of the possible combinations of ligands is presented during the education. Despite this fact, CFSs are capable of learning correlations in the presentations characterizing the "normal" presentations and become tolerant to them. CFSs are also capable of signaling as abnormal deviations from these normal configurations. The responses against abnormal presentations will be discussed in the next section.

4.7.2.2 CFSs consistently detects abnormal presentations

CFSs become tolerant towards a wide range of presentations, even if the exact configuration has not been presented in the education process. Can the capacity of generalizing compromise the detection of abnormal configurations? In the following set of experiments the perturbation imposed was presented ligands from blocks 1, 2, 5 and 6. In spite of the fact that all ligands have been presented during the education stage, blocks 1 and 2 have never been presented together with blocks 5 and 6.

As can be appreciated in the histograms in Figure 4.62 the abnormal presentation of ligands decreases the frustration in the dynamics. In Figure 4.62A the red lines refer to the dynamics resulting in the presence of the abnormal presentation, while the black lines refer to the system in the calibration stage. In Figure 4.62 B two different histograms (in blue and black) corresponding to the dynamics in different "normal" presentations are displayed.

Histograms in Figure 4.62A seem to indicate that a strong response against the abnormal presentation should be expected. However, it is important to bear in

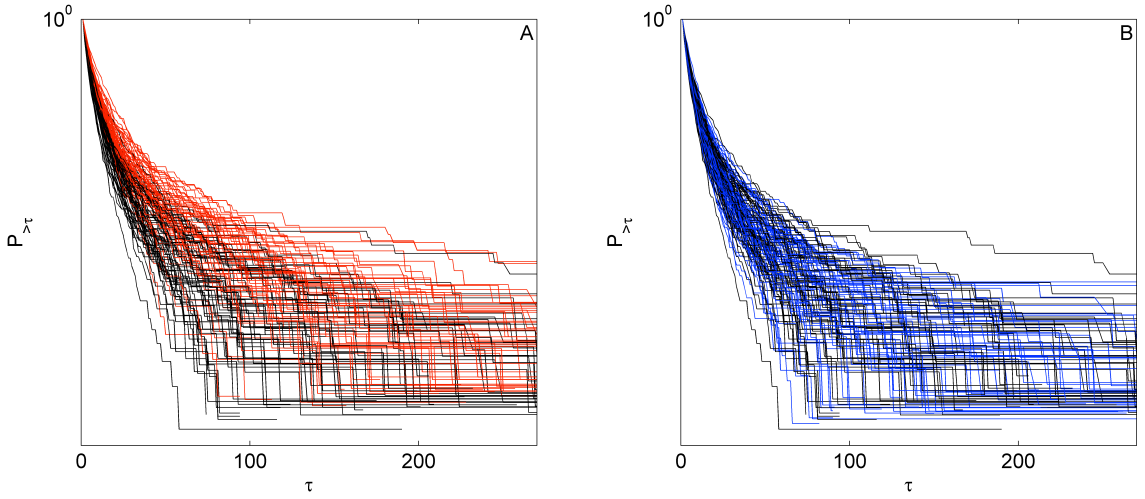


Figure 4.62: Histograms for the probability that each presenter establishes a conjugation longer than τ iterations, for each presenter in the population and registered: (Black) in the calibration stage, (Red) after an abnormal presentation, (Blue) during the monitoring stage without abnormal presentation (hence, similar to histograms registered during the calibration).

mind that the $f^o_{i,>\tau}$ is selected from their maximum values registered over all systems simulated during the calibration phase. Hence, the number of presenters that have $\mathcal{R} \geq 1$ is smaller than is could have been expected from a naive analysis of these histograms. The number of presenters with $\mathcal{R} \geq 1$, $n_{\mathcal{R}\geq 1}$, for all systems and the sum of the deviations from $f^o_{i,>\tau}$, D, are registered at τ_1 are shown in Figure 4.63. The remaining results are presented in Table 4.7.

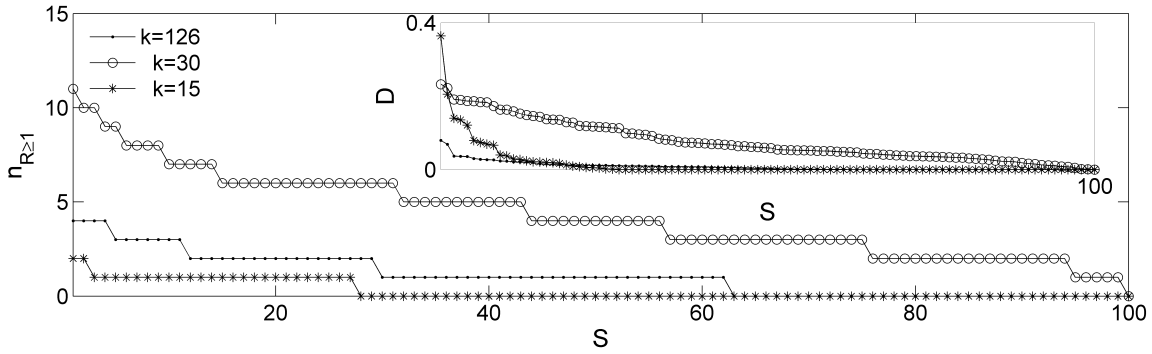


Figure 4.63: Number of presenters with $\mathcal{R} \geq 1$, $n_{\mathcal{R}\geq 1}$, and the corresponding sum of deviations from $f^o_{i,>\tau}$, D, in each system S and for different connectivities.

CFSs are capable of performing detection of abnormal presentations. There is an optimal value of connectivity for which detection of abnormal combination of

Table 4.7: Results for Detection of Abnormal Presentations ($\overline{n_{\mathcal{R}\geq 1}}$±std).

Presented Blocks	τ_1	τ_2	τ_3
			k=15
1, 2, 5, 6	0.3±0.5	0.4±0.7	0.6±0.7
1, 2, 3, 4+3, 4, 5, 6	0.1±0.4	0.2±0.5	0.4±0.6
			k=30
1, 2, 5, 6	4.3±2.3	4.8±2.2	4.3±1.9
1, 2, 3, 4+3, 4, 5, 6	0.1±0.3	0.2±0.4	0.3±0.5
			k=126
1, 2, 5, 6	1.1±1.1	1.6±1.3	1.7±1.4
1, 2, 3, 4+3, 4, 5, 6	0.04±0.2	0.14±0.4	0.22±0.4

ligands is stronger. For systems with k=15, there are many fluctuations in the dynamics even during the calibration stage. Consequently, calibration thresholds become more demanding which makes detection difficult. For k=30, fluctuations have a smaller impact in the dynamics leading to better detections.

Another point that is worth mentioning is that the individual agents' responses are, on average, considerably less intense than in the case of the detection of foreign ligands. However, contrary to what happens in that case, many agents can respond to a perturbation, which makes the response a more collective phenomenon. Mechanisms of quorum sensing could then be useful to amplify these responses.

4.7.2.3 The ordering of ligands is crucial for detection

The activation of agents is intimately related to the experience of long conjugations formed by each presenter during the calibration stage. Consequently, if a presenter displays many different ligands, a wider range of typical dynamical behaviors should be expected, which tends to increase the calibration threshold associated to that agent. In order to reduce the variability in the ligands they present, simple ordering strategies were implemented. These are important to achieve good responses in the monitoring stage. Figure 4.64 shows the ligands displayed by the same presenter, throughout all stages, for a random or an ordered sequence of ligands in the presentation. While for the random case a single presenter could display almost all ligands available, when ordering is applied only 6 ligands are shown. Similar results are obtained for the remaining presenters. Thus, for random presentations, the ligands that are less frustrated will increase $\mathrm{f}^{o}_{i,>\tau}$ of all presenters. This increase can

be seen in Figure 4.65 in which $P_{>\tau}$ as function of the presenter is represented, for a calibration phase performed with a random or a ordered presentation of ligands.

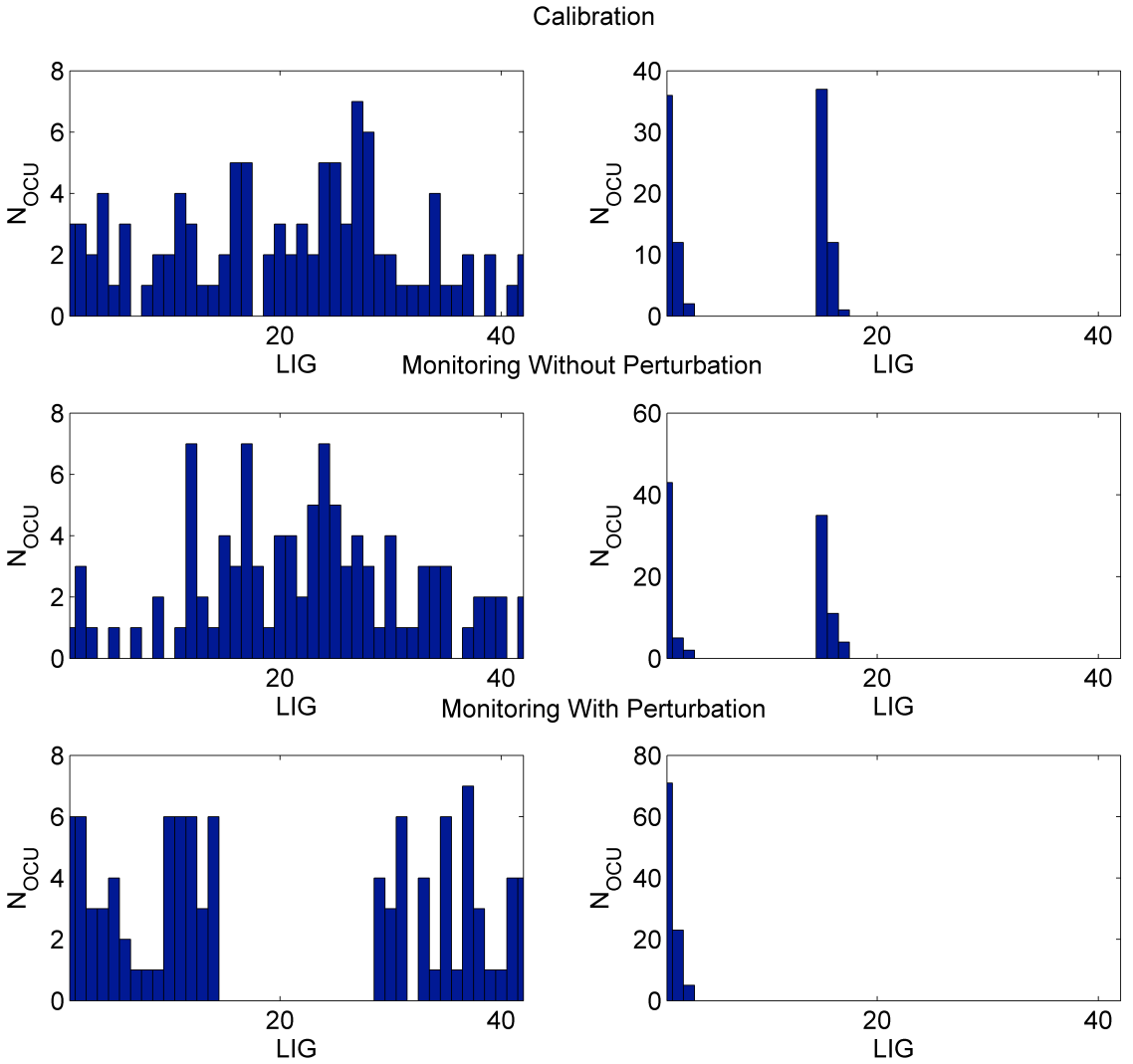


Figure 4.64: Histograms representing the number of times each ligand was presented by a given presenter when (Left) the ligands are assigned to presenters in a random order or (Right) ranking ligands in increasing order. (Top) histograms obtained for the calibration state, (Middle) after the monitoring stage without abnormal presentation and (Bottom) after an abnormal presentation of self ligands. It is clear that an ordering scheme reduces the number of different ligands each presenter will display. Similar results are obtained for the remaining presenters.

Non-ordered presentations of ligands produce activation criteria that are close to those used in section 4.4, in the detection of foreign ligands. In fact, in this case all agents have thresholds close to the maximal values of $f^{o}_{i,>\tau}$. As a result, the

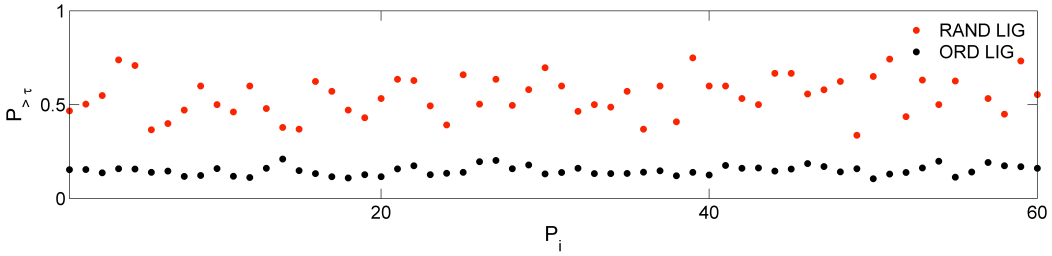


Figure 4.65: The maximal probability for establishing conjugations lasting longer than τ iterations registered after the calibration stage and for each presenter when ligands are randomly distributed among the presenter or distributed according to an order.

$f^{o}_{i,>\tau}$ values per presenter increase which has a dramatic effect on the performance of the detection of abnormal presentations. Figure 4.66 presents the number of presenters with $\mathcal{R} \geq 1$ in the presence or absence of perturbation - red and black lines, respectively - and considering a random or an ordered distribution of ligands by presenters.

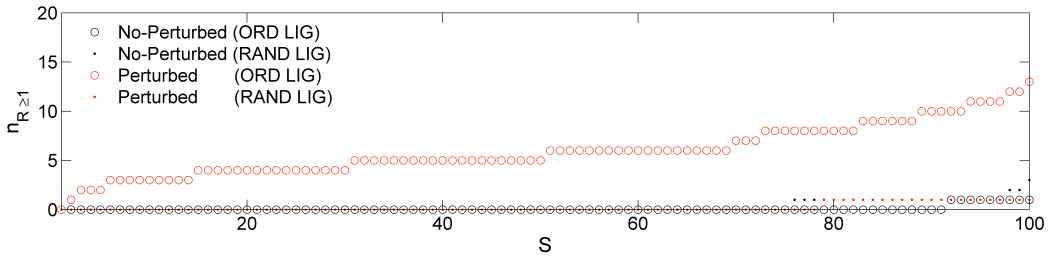


Figure 4.66: Number of presenters with $\mathcal{R} \geq 1$, measured at τ_1, $n_{\mathcal{R}\geq 1}$, as a function of the system S, when ligands are randomly distributed by presenter agents or are distributed according to an ordering scheme.

If ligands were randomly distributed by presenters, 0.03±0.2 presenters have $\mathcal{R} \geq 1$, on average, against the 6.00±2.3 presenters with $\mathcal{R} \geq 1$ for the system in which they are ordered (considering k=30 and τ_1). This result points out the importance of the correct selection of $f^{o}_{i,>\tau}$ per presenter. In systems in which ligands are ordered, each presenter displays only a small number of different ligands, and $f^{o}_{i,>\tau}$ is representative of the dynamics established by the ligands displayed by these presenters. If the dynamics of some ligands are not as frustrated, presenters that show these ligands have $f^{o}_{i,>\tau}$ values that can barely be overcome. If all the presenters can display all the ligands available in the system, it is highly probable that all of them have $f^{o}_{i,>\tau}$ which prevents presenters from responding to small changes in dynamics. Consequently, the system loses its capacity to detect abnormal presenta-

tions.

4.7.2.4 CFSs detect abnormal repetition of ligands.

Another study concerning abnormal presentations involves responses to a repetition of blocks of presented ligands. To study the response to an abnormal repetition of ligands, the presented blocks were doubled and presented in sequences such as 1123 and 1122. In this case the effect of the repetition of the ligands adds to the presentation in different contexts. For example, in the presentation of blocks 1133, blocks 1 and 3 had already been presented together, in contrast with the combination 1166 in which block 1 had never been presented with block 6. Figure 4.67 shows the number of presenters that have $\mathcal{R} \geq 1$ for different simulations, for presentations in which two blocks were repeated. The black line represents the response in the absence of the perturbation, while the red and the blue lines to systems in which blocks were repeated. In red are pointed systems that combine blocks that had already been presented together, while in blue are represented systems that add two effects, the repetition of ligands and presentations in different contexts.

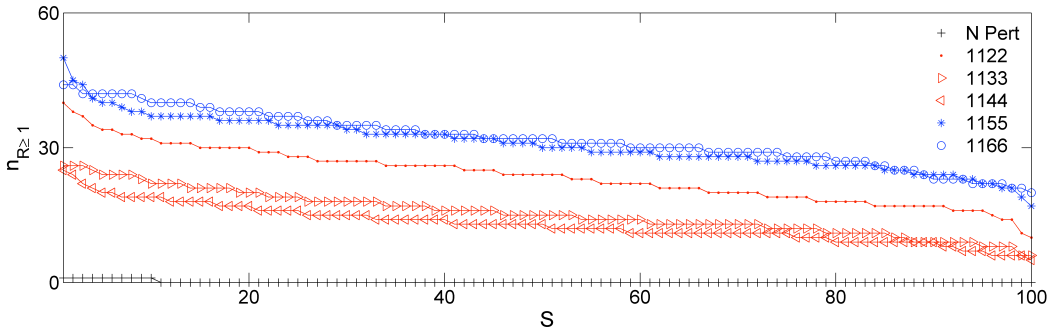


Figure 4.67: Number of presenters with $\mathcal{R} \geq 1$, measured at τ_1, $n_{\mathcal{R}\geq 1}$, as a function of the system S, for connectivity k=30 and with two repeated blocks.

Responses are stronger when the repetition is combined with the abnormal presentation of ligands: on average, 32.0±6 and 30.8±6 presenters were activated for the combination of blocks 1166 and 1155, respectively, at τ_1. Smaller responses are obtained for presentations with a repetition of the fixed block 1133 and 1144: 15.4±5 and 13.0±4 presenters have $\mathcal{R} \geq 1$ respectively, also at τ_1. All responses against the repetition of ligands are accomplished with total tolerance relative to the system in the absence of perturbation in which case none of the presenters was activated: 0.1± 0.

The response decreases with the decrease of the number of blocks repeated. The repetition of two blocks originates stronger response than if only one block is repeated. Figure 4.68 shows the number of presenters with $\mathcal{R} \geq 1$ as a function of the system, for different presentations with only one block repeated. The correspondence of colors is the same: the black line represents the absence of perturbation, while red and blue lines show perturbed systems with only repetition of ligands or the repetition of ligands together with abnormal presentation, respectively.

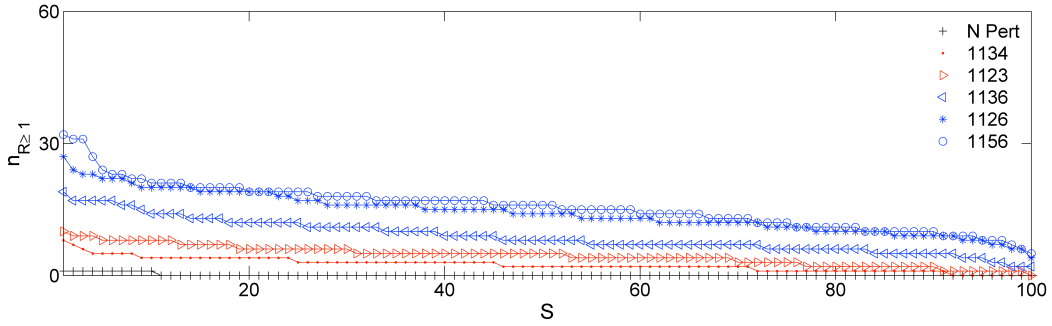


Figure 4.68: Number of presenters with $\mathcal{R} \geq 1$, measured at τ_1, $n_{\mathcal{R}\geq 1}$, as a function of the system S, for connectivity k=30 and with only one block repeated.

Also in these systems, presentations combining the repetition of blocks with an abnormal presentation have stronger responses: on average, 15.6±5, 14.4±5 and 8.9±4 presenters are activated for the combinations 1156, 1126 and 1136, respectively, at τ_1. These responses decrease to 4.2±5 and 2.4±2 presenters activated for the presentations 1123 and 1134, respectively.

These results suggest that the responses obtained depend on the blocks presented together with their repetition. Combinations of blocks that combine abnormal presentations with their repetition have stronger responses when compared to presentations that only repeat blocks. In spite of the different responses obtained, all CFSs performed detection with tolerance towards self.

4.7.3 Abnormal Presentations of Different Self Ligands and Generalization: Final Discussion

CFSs are capable of learning patterns of normality from a large set of possibilities. CFSs are capable of inferring information concerning the simultaneous presentation of ligands. In this sense CFSs have generalizations capabilities, learning from a small sub-set of "normal" configurations, configuration towards which the sys-

tem should remain tolerant. Simultaneously it becomes reactive towards abnormal presentations.

In a summarized way, in this section it was shown that:

- CFSs are capable of generalizing presentations within a large set of "normal" configurations and become tolerant to them;
- Presentations that do not belong to the educated pattern of presentations are recognized as abnormal and a reaction is triggered against them;
- There is an optimal value of connectivity that ensures tolerance towards self, but reaction against abnormal presentations.
- Presentations that combine abnormal presentation due to the repetition of ligands and anomalies in context are easily detected because of the combination of both mechanisms of detection.

This last section of results finishes the presentation of the main results concerning the potentialities of CFSs. These combine the perfect discrimination self/nonself, the ability to produce homeostatic responses and with the capacity of generalizing legitimate patterns from an arbitrary large set. All these features open the possibility of developing applications in different fields involving anomaly and intrusion detection.

5

The Cellular Frustrated Approach: Final Discussion

The method developed in this thesis uses a new conceptual approach to understand cellular interactions in the adaptive immune system and proposes a new direction in artificial intelligence. The inspiration to the cellular frustration framework arouse from a distant problem in computational optimization, namely the stable marriages problem (SMP) [52]. This problem was first addressed by Gale and Shapley in 1962 [53]. In the stable marriages problem a set of men and women have to be paired in a stable arrangement so that no men or women can find a better partner that also accepts them. Stated in this way, the problem resembles the cellular frustration scenario described in Section 2.3.3. However, the problem that has long been concerning computer scientists consists in finding efficient algorithms capable of finding the stable configuration in polynomial time. This is a nontrivial problem because for some instances of the game the problem is NP-hard [54], in which case no algorithm can find a solution in polynomial time [55]. In those cases, there would be individuals in a population that cannot be arranged in a stable pair, at least within a reasonable time. However, at the same time, some individuals may easily find a stable matching, as when perfect matches exist in a population - i.e., when a man and a woman prefer each other, ranking each other in the top of their ILists. This observation led the supervisor of this thesis to formulate models for which such a dramatic difference in the dynamics could lead to different outcomes for the different individuals in the population. It became apparent that in any such model, the different outcomes would have to depend on the duration of contacts, a measure of pairs' stability. The duration of contacts in immunology [15], or the duration of matings in evolutionary biology [16], would have to play a major role, and indeed the individuals' fitness can be understandably linked to matings stability

[56, 57], and likewise conjugation lifetimes' are well acknowledged in immunology as being associated to different cellular effector functions [25].

At this point it should be mentioned that some theoretical approaches had already attributed importance to the duration of intermediate processes before major signals are triggered [12]. In the context of immunology, Mckeithan proposed that the kinetic proofreading could be essential to account for the highly specific T cell activations [13]. In McKeithan's only the interactions between two cells (an APC and a T cell) are considered and consequently this model is certainly important to describe how cells distinguish the several ligands they interact with. However, it cannot be produce context dependent responses, like the abnormal self-detection we described. These properties are collective properties and consequently can only result from an emergent property of the collective set of cells. In the cellular frustration framework this results from the collective frustrated dynamics of the system. In fact the cellular frustrated dynamics also embodies a generalized form of a kinetic proofreading mechanism, first found in [16], and discussed in the context of the kinetic proofreading scheme in [15, 30]. This amplification mechanism has new properties. In particular it is context dependent, whereas in the classical description the amplification constant depends only on (fixed) kinetic affinity constants [30]. This is an important property conferring robustness to the discrimination task.

The cellular frustration framework uses the frequency of stable contacts as a threshold for cellular activation. Grossman and collaborators [58, 59] had already proposed that cells in the immune system should respond when the level of stimulation they were submitted to exceeded a threshold. This was inspired in the neuronal system, which sparked inspiration among immunologists [60–63]. In the tunable activation thresholds scenario, thresholds can vary on context and be different for each cell. Cellular stimulation would be a function of the avidity of interactions and it would result from the integration of multiple signals. It could also depend on the sharpness of the stimulation [58], which suggests that pathogens could use smooth invasion strategies. Hence, to a certain sense, the tunable activation thresholds hypothesis proposes dissociating foreignness from the peptide, which clearly is not the case in the cellular frustration discrimination of self from nonself. It should be noted that the tunable activation threshold hypothesis remained largely as a verbal hypothesis by the original authors, and consequently it did not show, for instance, that robust protection could be achieved in this way. This has nevertheless been suggested by further works in the artificial immune systems' community, where in-

teresting results, although with no indication of perfect discrimination, have been achieved [64, 65].

The cellular frustration framework also uses activation thresholds that are tuned during repertoire education, and which can be different for each cell. The main difference between the two approaches is on the mechanisms of cellular stimulation. In the cellular frustration approach, stimulation depends only on the most stable contacts, forcing the T cell repertoire to be organized so that cells engage in a maximally frustrated dynamics. This has numerous consequences, and in particular anergy and costimulation are explained differently. In the cellular frustration framework they are intimately related to the elimination of stochastic fluctuations to achieve perfect self nonself discrimination, whereas in the tunable activation thresholds anergic T cells can be used to suppress co-activated cells [59].

The inspiration arising from the stable marriage problem was extremely prolific. Not only it suggested a different way of addressing cellular interactions, but also offered new explanations for a number of well documented phenomena. First, it became natural to admit that all cells could play more symmetrical roles than usually assumed. All cells should display ligands and use receptors to read information displayed on the other cell's membranes. This represented an original assumption, which is not even too revolutionary, since as it was discussed in this thesis the information displayed by T cells to APCs can be much more limited than the information displayed by APCs to T cells. However, so far all literature focused on the information displayed by APCs to T cell receptors, which may have also been due to the fact that experimentalists have always questioned how the information presented by MHC molecules triggers an effector function. The more symmetrical role played in cellular interactions needs to be tested and can be seen as a prediction or a requirement of the cellular frustration approach to immunology.

Although involving a different set of agents, antigen and antibody, a proposal initially put forward by Niels Jerne [60] on the formation of idiotypic networks, also requires that each agent has two components, one to read antigenic information, the paratope, and the other displaying it, the epitope. Hence, in this case as well, each agent works as both, the presenter and the detector [60]. This approach was also considerably prolific [62], and drove a considerable range of work [66–71], and it even had an impact in artificial intelligence [72]. The field of idiotypic networks has nevertheless failed to find experimental support, and an interesting account of the rise and fall of this scientific paradigm can be found in [73].

Our approach has marked differences with the idiotypic approach, not only at the level of agents and mechanisms involved, but also at the level of concepts. For instance, while the duration of contacts is crucial to induce perfect tolerance and strong reactivity against nonself in the cellular frustration, it plays no role on idiotypic network approaches. Furthermore, in the cellular frustration framework self-nonself discrimination plays a special role, whereas idiotypic networks are mainly concerned with interactions with self [62, 66]. This however, does not mean that idiotypic networks cannot explain antigenic elimination. Indeed, one of the achievements of the idiotypic network formulation is that it offers a simple conceptual view on different responses to antigen, ranging from a weak response in a naive state, a strong response in the immune state, and a suppressed response in the tolerant state [74, 67]. Different responses depend on the different relative concentrations of the several antibody linked to the antigen. What I believe the idiotypic network formulation has difficulty in establishing is in discriminating robustly when to deliver a strong or a weak response in face of the introduction of a new antigen determinant. This, I believe, limits the applicability of idiotypic network approaches to anomaly detection, which indeed have never found applications in the artificial intelligence field in relation to anomaly detection. Rather, most sought applications have been related to clustering [72].

An alternative approach to the adaptive immune system that has been tested in artificial intelligence [75], is the crossregulatory model proposed by J. Carneiro [76]. This model got its inspiration in the idiotypic immune system although it is concerned with the modeling of T cell activation and the ability to maintain tolerance in the periphery in the absence of pathogens. Similarly to the idiotypic network approach, it also uses the idea that the activation of the population of effectors can be suppressed by another type of cells - the regulatory T cells - if they are more numerous. In that way two cell types are required (in the idiotypic network tolerance was achieved due to the interaction of anti-idiotypes upon idiotypes) to achieve tolerance, and in the absence of regulatory T cells, autoimmunity or nonself detection would be triggered. Several variants of this idea were studied in a series of papers[76–78], to better meet experimental observations. In our work, tolerance is achieved in a different way, although both approaches achieve tolerance due to the presence of a third cell. However, the cellular frustration induces tolerance without requiring the elimination of cells, whereas, both the crossregulatory model or idiotypic network approaches require a continuous elimination of cells and replen-

ishment. Since T cells can live up to 10 years in humans [79], this suggests that probably a tolerance mechanism not requiring cellular elimination may be more appropriate. Another point worth considering is that so far the cellular frustration model did not require a regulatory T cell to achieve perfect tolerance. This may look problematic at first sight, since it is known that regulatory T cells are essential to avoid autoimmunity in mice [80]. However, it is possible that regulatory T cells become either essential or simply beneficial, when other immunological phenomena are considered. For instance, this could be related to the clonal expansion of the T cell repertoire, or the adaption to time varying perturbations. Hence, it cannot be ruled out that the cellular frustration framework could not benefit from inspiration from the crossregulatory modeling work when further immunological scenarios are considered.

The stable marriages problem also called a special attention to how cellular interactions should be modeled. In the stable marriages problem all individuals attempt to optimize a "preference" function. This suggested considering that, in a population, individuals would continuously perform decisions to accomplish this goal and that only when sufficiently stable pairs are formed, outcomes, like reproduction or effector functions, would be triggered. This was proposed in [16] for a model for sympatric speciation, and in the seminal paper relating this approach to immunology [15]. This modeling approach allowed the identification of frustration in cellular interactions as an essential ingredient to establish tolerance as discussed in [15].

In this respect it should be mentioned that frustration is a well-known concept in physics. It was first found by Wannier in 1950 [81] when studying the Ising spins in a triangular lattice, having led to an intense field of research that still lasts to this day. The term frustration was likely coined for the first time by G. Toulouse in 1977 [82]. In this field, researchers have been mainly concerned with the unusual physical properties that the existence of multiple ground-state configurations could produce. Unusual physical properties, like the slow magnetic relaxation in spin glasses, are mainly dynamical properties, stemming from the fact that the system never stabilizes in a single state, even at zero-temperature [81].

In our work frustration operates in a similar fashion, in the sense that it requires that no stable pairs are formed if perfect tolerance is to be achieved. This was the reason why F. Vistulo de Abreu coined this scenario"cellular frustration". However, cellular frustration gives a special attention to the time duration of conjugations as only stable pairs trigger effector functions. This establishes a clear difference with

the approach in physics, which is concerned with macroscopic properties. Furthermore, in the cellular frustration it became clear in [20] that if the immune system is to be tolerant to self, then it should be highly organized in the sense of maximizing frustration so that a characteristic lifetime could be defined for interactions involving cells presenting self-peptides. This led us to propose a new principle of organization of a complex system which should be relevant to the immune system. This was called the principle of maximal frustration and it should guide repertoire education in the thymus.

The application of the idea of frustration is not new in the immunological literature. Indeed Bersini and Calenbhur [83, 84] used frustration to promote the appearance of chaos in idiotypic networks. They also suggested that tolerance could benefit from frustration in these models. The definition of tolerance is nevertheless different in both approaches, as in idiotypic network models no role is played by the duration of contacts. Furthermore, in the cellular frustration model the aim is not only on promoting tolerance, but also on being able to maintain extreme reactivity against nonself. The principle of maximal frustration establishes a quantitative criterion for reacting or not reacting, which has a clear consequence on the performance in the discrimination task. For instance, in poorly educated T cell repertoires, perfect (or almost perfect) tolerance towards self could be maintained even if reactivity against nonself would be poor. Hence, the suggestion that the immune system wants to be maximally frustrated became a natural outcome of the cellular frustration approach[20].

The mathematical approach to the stable marriages problem provided also inspiration for mapping the information sensed by T cell receptors on APC ligands in a different way. In fact, in most theoretical models in immunology [49, 76, 85], the affinity controlling the strength of interactions is seen as a continuous function in the space of peptide sequences. On the contrary, mating preferences in humans were considered to be highly diverse in the SMP, with preference lists ranking individuals of the opposite sex in potentially arbitrary orders. As it was discussed in Subsection 2.3.3., this can also be a reasonable approach in the immunological context, given the intricate diversity of generation mechanisms of T cell and B cell receptors. Interestingly this view on how the information in T cell receptors is mapped is crucial to achieve perfect self-nonself discrimination in the cellular frustration framework, because it allows different cells to establish interactions of a completely different strength with two different antigen. This has also an important immunolog-

ical implication because if offers a new explanation on how crossreactivity promotes specificity in immunological responses. Indeed, if receptors diversity allows each cell to perceive ligands' space using completely different topologies, then the cellular frustration framework guarantees that a finite fraction of the T cell repertoire can interact with a foreign ligand, which guarantees prompt and specific responses. It should be mentioned that crossreactivity seems to work against building very specific interactions. However, in an influential paper [86], Don Mason argued that immunological interactions had to be extremely crossreactive, as otherwise the number of different T cells required would occupy a volume many times greater than the actual body size. Any immunological mechanism should rely of extensive crossreactivity to gain robustness. Otherwise it would need to explain how extremely specific cells would efficiently encounter their cognate antigen [87].

The previous mapping in ILists has also important implications in the artificial intelligence field. Indeed, it opens the door to a new type of artificial intelligence algorithms for anomaly detection. Anomaly and novelty detection are demanding classification tasks. Intrusion detection can be considered even harder, given that the intruder can have an active role. The main difficulty with these tasks it due to the high dimensionality of the space that needs to be considered. The number of different configurations characterizing the system's normal behavior can be potentially very large. However, the number of configurations characterizing an abnormal behavior can certainly be even larger. Algorithms to address these problems thus need to have generalization capabilities. All methods use some a priori hypothesis on the data. Some are more explicit than others. For instance clustering methods assume that a certain metric is good to capture neighborhood properties in a data set, different metrics being more suitable for some problems than others [88, 89]. Similarly, many probabilistic density function estimation methods assume that distribution functions are approximate gaussians in regions of the space, and in this way they classify as outliers events whose frequencies are far from the expected frequency, beyond some threshold value. Other methods, like neural networks, have less explicit assumptions. In a certain sense they act as black boxes. They are known to reproduce perfectly logical functions, and they can also be good at performing function approximations [90, 91]. Neural networks, like other methods such as support vector machines [88, 92], can perform a complex optimization classifying points in a continuous space in classes. These methods assume nevertheless that this classification is continuous, in the sense that most points in a close neighborhood are classified in the same way.

This assumption may not be appropriate in many practical applications, such as in text classification, as in that case single substitutions can change a correctly spelled word into a misspelled word. Indeed, in this case, one should expect that words are sparsely distributed in space, correctly spelled words being distant points in an almost empty space.

The cellular frustration approach offers a new approach to data classification that can be useful to tackle problems in which "self-data" is sparsely distributed in a high dimensional space. Indeed, the method we presented is capable of classifying correctly self-data points as self and react when any other point is presented. At the same time the cellular frustration approach also classifies patterns of self-points, depending on whether they have been presented during the education process or not. Clearly this part of the task was not so thoroughly studied in this thesis, but simple mechanisms have been identified that show that cellular algorithms should be capable of detecting when sets of points that are consistently presented together during the education phase, are absent in the detection phase. This means that the cellular frustration algorithm can work as a complex correlation function calculator of sparsely distributed data points. I believe that this type of artificial intelligence algorithm is new as it performs an anomaly detection task different from any other method I know in the literature [7, 93], and using a conceptual different method of calculation.

A new understanding of the phenomena of positive selection in the thymus, and costimulation and anergy in the periphery has also been suggested in this thesis. So far it has been difficult to explain why these phenomena are required for a proper function of the adaptive immune system. However, our proposal is not completely unexpected. Indeed, it should have been expectable that positive selection could be required to avoid having useless T cells in the repertoire. However, it has been difficult to prove with theoretical quantitative models [94–96] that without positive selection the adaptive immune system could fail its function. Similarly, costimulation and anergy have long been associated to mechanisms required to increase specificity and tolerance, respectively. However, most theoretical models in the literature do not require them to perform self-nonself discrimination [48, 49]. Alternatively and in clearer contrast with our proposal, Janeway's infectious nonself model [97] and Matzinger's [98] danger model, propose that costimulatory ligands signal the presence of infection or danger signals in the host [43]. These should originate from outside the lymph node, not being upregulated during the sequence of dynamical

interactions in lymph nodes as the cellular frustration framework proposes.

The cellular frustration framework also proposes that the strength of interactions is not reduced in magnitude during negative selection. Rather, it is the direction of these interactions that is modulated. I.e., T cells receptors should have the highest affinities towards ligands displayed by APCs whose receptors sense the ligands displayed by these T cells with lowest affinities. This is a new proposal that calls attention to the ligands displayed by T cells to APCs receptors.

It should also be mentioned that the present thesis did not address important issues concerned with selection criteria for data presentation. This corresponds to modeling how APCs select which peptides are presented in MHC molecules. In an artificial intelligence perspective, this can be seen as a preprocessing data stage. Some work has been done in this respect in the artificial immune systems community using the danger theory inspiration [99, 100]. It is possible that this type of algorithms could be useful for selecting which data APCs should display in order to render algorithms more efficient. This may indeed be necessary since the number of cells that can be considered in numerical algorithms is considerably smaller than in the actual immune system.

This thesis had an important concern: to build a consistent theory that could, under a single set of initial simple assumptions, explain a wide range of phenomena in immunology. As guiding inspiration it was assumed that the adaptive immune system should be capable of performing self-nonself discrimination without errors, at least in certain limits. This requirement is clearly grounded to the view that the adaptive immune system is a robust and flexible anomaly detection system. The purpose was ambitious, because the vast range of well documented phenomena we addressed seemed conflicting, even paradoxical. Consistency is extremely important in any modeling approach. Quoting Einstein, a model should be the simplest but not simpler. In this sense I feel that having been able to propose explanations for phenomena like positive selection, costimulation and anergy, without having built models specifically addressing these issues seems an encouraging result. Science however is not merciful as only those predictions agreeing with experiments survive. Furthermore I would add that technology can also be ungrateful, as only those methods and products that make their way into our lives, live. However, in this respect the cellular frustration framework gave auspicious signs of a successful future. This thesis unveiled mechanisms that guarantee that two main modes of anomaly detection - detection of nonself sequences and detection of the presentation

of abnormal combinations of sequences - can be performed. However, only future work can confirm in full extent the validity of our bold initial pretensions.

6

Personal Perspective

One never notices what has been done;
one can only see what remains to be done
Marie Curie, 1894

The development of an anomaly detection system to monitor the behavior of complex systems is extremely relevant and challenging. Complex systems are present in a wide range of fields. A common anomaly detection system is the antivirus software that runs in our computers. When we think about how it works, one concern comes to our minds - what happens if the antivirus fails? Nobody desires a virus infecting their computers, nor an antivirus software that acts as a virus, continually using computer resources even in the absence of an anomaly. Until now, these are considered the two sides of the same coin. Ideally, an anomaly detection system should detect *any* anomaly in the system with zero false alarms. Can a monitoring system offer perfect detections? Yes, I think that it is possible. Actually, I was not the first person with this belief. Regarding perfect detection in the anomaly detection systems, my supervisor always mumbled: "nothing less than perfection!" and he was right.

Now, looking back, it might seem unreal, even to me, that we started this research only with the strong conviction that a system that accomplishes perfect anomaly detection was possible. Additionally, we had the belief that the solution was a new organizing principle of complex systems and two plausible assumptions. We thought that the interactions between agents could be modeled as decisions instead of instantaneous reactions and that the time of interactions should play a critical role in the triggering of a response. The development of an anomaly detection system

in these conditions was exciting but not an easy task. A hard work of development was required to achieve these results. Almost every day, a new idea was discussed and tested in order to find the right direction to follow in the research. An amazing number of possibilities was studied; most were abandoned, because they did not meet our requirements. Nevertheless, in the midst of unsuccessful results, the first positive results started to appear. The first important achievement was the understanding of the reactive and tolerant state in this framework. Here, a tolerant state is built with maximally reactive agents which interact in a frustrated dynamics. From the interactions established in this dynamics tolerant or reactive states emerge. These concepts are not seen as attributes of each agent but as emergent properties of the system. Tolerance and reactivity were understood in an unconventional way and the apparent paradox between maximal reactivity and perfect tolerance disappeared.

This new perspective set the direction regarding the dynamics that should be imposed in anomaly detection systems and another result appeared: perfect intrusion detection in perfect systems. This was a very encouraging result at that time. It showed that, at least in principle, perfect detection was possible and that work was going in the right direction.

Having obtained the result that perfect detection is possible, the next step was to explore how to generalize this result to an arbitrary system. This generalization to every arbitrary system would allow different applications in different fields. However, how this could be done was not clear for a long time. After several unsuccessful attempts, we decided to look at the real immune system. The question was: how does the immune system address this problem? Firstly, we introduced in the method the random generation of detectors' receptors and the education process inspired in Immunology. These two concepts were crucial to the selection of an extended repertoire of detectors that ensures frustrated interactions among agents. However, more or less education and diversity in receptors resulted in no-detection rates around 20% for intrusion detection. These values were very far from the expected 0%. Something crucial was missing. But, what was missing? Which were the mechanisms responsible for ensuring perfect detection?

Again, the idea was to focus on the immune system and to search for answers. These answers were the anergy and the costimulation mechanisms. Both are present during the monitoring process in the body, so they could play a role in the detection process. Actually, in the model they were crucial. Anergy and costimulation solved the problem of imperfect detection. Their implementation was responsible for going

from a no-detection rate around 20% to 0%. *Voila*, what seemed almost impossible in the beginning of this work was achieved: an anomaly detection system capable of performing perfect self/nonself discrimination and abnormal self presentations simultaneously and with the same mechanisms.

Thus, perfect anomaly detection is possible in systems with arbitrary diversity and independently of the size of the system considered. However, to achieve this result detectors' diversity should be taken into account, so that different affinities towards presenters are established. Additionally, positive and negative selection are required to increase the frustration of the conjugations among agents. Finally, anergy and costimulation are crucial to the monitoring stage. While costimulation signals that presenters decrease the frustration in their interactions during the monitoring stage, anergy ensures that the increase in the stability is not due to a single detector. It is amazing how the work that took 4 years to be developed is now reduced to a single paragraph. The novelty of the work and the remarkability of the results obtained contributed for the submission of a patent which credits the method [101].

Even if this work may seem the end of a story, this is definitely not true. This is only the beginning of the development of a promising framework. Until now, the goal was perfect discrimination in perfect systems, perfect discrimination in arbitrary systems, perfect discrimination in everything. Now that perfect discrimination has been achieved, different other issues start to pop up. Personally, I look forward to understanding the role of the T_{REG} in this framework. I am also interested in the mechanisms involved in the termination of the immune responses and in the mechanisms responsible for the returning to the equilibrium state after a perturbation. I have already started this latter study, but no complete results have been achieved. Much work remains to be done in these systems. The quotation that starts this chapter completely describes my feeling after this thesis: one never notices what has been done; one can only see what remains to be done.

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