

Immunology as a Metaphor for Adaptive and Distributed Information Processing

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Abstract—How can one effectively exploit the adaptive and distributed information processing characteristics of the immune system for the purposes of computation and engineering problem domains? The field focused on this problem is artificial immune systems, and this work provides a novel hierarchical framework as to how such work, may proceed from at least three similar, although distinct directions.

Keywords—Research Project, Computational Intelligence, Artificial Immune Systems, Hierarchical Framework, Distributed, Information Processing, Adaptive Models, Distributed, Decentralised, Autonomous

I. INTRODUCTION

Artificial Immune Systems is the study of computational information processing inspired by the structure and function of the immune system. The field is young as a subfield of computational and artificial intelligence, although even with its potential and youth, the field is rapidly becoming stale, given the lack of suitable application domains and quintessential algorithms that set the field apart. In considering this open problem a perspective of the framework is proposed that considered information processing at multiple scales (cellular, tissue, system), which provides promise toward the effective exploitation of the inherent parallelism and distributed information processing offered by the inspired biological system. Section II motivates the general research including the field of scruffy artificial intelligence known as computational intelligence, and the specific field of artificial intelligence and the open problem being considered. Section III considers the background for the problem, specifically focusing on the cell-based immunological theories, which much of the field of AIS is based, and some biological background (physiology, cell mobility and immunization) that provide the foundation for the hierarchical perspective. Section IV considers a system-environment stimulus response relationship between the immune system and molecules to which it responds. This situated, agent-like relationship provides broad problem and context for the information processing across the hierarchical framework, specifically acquisition of information from an environment in a piece-wise manner. The framework is explored in section V, focusing on the so-called ‘low hanging fruit’ models at each of the three levels. Finally, section VI strongly urges the adoption of the framework to

generally move the field forward, suggesting a set of basic perspectives for exploiting the hierarchy and scaled information processing characteristics at each level, and some general, although likely suitable application problem domains that apply across these scales.

II. MOTIVATION

This section motivates the research project. The section starts with a gentle introduction into the general field of study (artificial intelligence), which is shown to be partitioned into the neat (statistical and symbolic), and the scruffy’s (non-statistical and non-symbolic), the latter commonly unified and known as computational intelligence. Biology is highlighted as a path into computational intelligence, by motivating the investigation of ‘intelligent’ strategies inspired by biology. A specific sub-field that exploits the mammalian immune system called artificial immune systems is introduced which provides context for the research project. The general problem of the project is discussed ‘distributed information processing’ inspired but the acquired immune system, and an integrated research methodology is outlined.

A. The General Field

The general field of study is the multi-disciplinary field of artificial intelligence (AI). Russell and Norvig provide a perspective that defines Artificial Intelligence by four categories: (1) systems that think like humans, (2) systems that act like humans, (3) systems that think rationally, (4) systems that act rationally [84].

Artificial Intelligence: *The general problem of artificial intelligence as a science is concerned with systems that think and or act like humans, or systems that think and or act rationally*

Acting like a human suggests a system can do some specific things humans can do, fields such as the Turing test, natural language processing, automated reasoning, knowledge representation, machine learning, computer vision, and robotics. Thinking like a human suggests systems that model the cognitive (information processing) properties of humans: general problem solver, models of the world. Thinking rationally suggests laws of rationalism and structured thought, such as syllogisms and formal logic. Acting rationally suggests

systems that do rational things such as agents, and rational agents. Luger and Stubblefield suggest AI as a subfield of computer science concerned with the automation of intelligence, and like other sub-fields of computer science has both theoretical (how and why do the systems work?) and application (where and when can the systems be used?) concerns [27].

Computer Science: *AI is a sub-field of computer science concerned with both the theoretical and practical concerns of automated problem solving*

They suggest the strong empirical nature to AI, such that although there may be a strong desire for mathematical analysis and the engineering perspective of employing intelligent artefacts in society, the systems themselves defy analysis due to their complexity. The machines and software themselves are not black boxes; rather we observe the systems interactions with their environment, then look inside the system and relate their structure back to their behaviour. AI is thus concerned with investigating mechanisms that underlie intelligence and intelligence behaviour. The traditional approach (so-called *good-old-fashioned AI* GOF-AI) has been to employ a symbolic basis for these mechanisms. A newer approach historically referred to as *messy* or *soft* artificial intelligence does not use a symbolic basis, patterning these mechanisms after biological or natural processes. This represents a modern shift in interest from symbolic knowledge representations, to inference strategies for adaptation and learning.

Neat versus Scruffy: *The neat philosophy concerned with formal symbolic models of intelligence that can explain why, whereas the scruffy philosophy is concerned with intelligent strategies that explain how (for example see [2])*

A modern name for the sub-field of AI concerned with sub-symbolic (*messy*, *scruffy*, *soft*) mechanisms is computational intelligence, which groups four such approaches: fuzzy intelligence, connectionist intelligence, evolutionary intelligence, and swarm intelligence [11,89]. Another popular and general name for the *strategy-outcome* approach is metaheuristics which evolved from the neater field of heuristics methods from operations research [14].

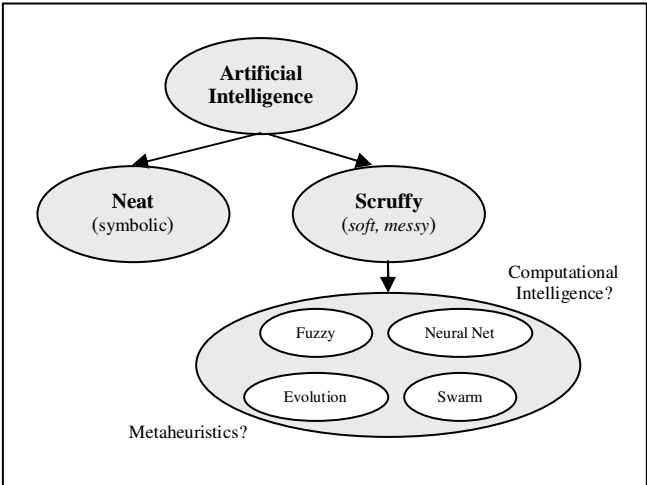


Figure 1 - Depiction of the decomposition of AI into neat and scruffy

An important perspective on scruffy artificial intelligence is the motivation for the strategy. Computers can only do what they are told, thus a consideration of computational intelligence is to invent, and to steal strategies from other fields of study – such as biology. The study of biologically motivated computational intelligence may be called biologically inspired computing [50], and is one of three related fields of natural computing [63,64,73]. Natural computing is an interdisciplinary filed concerned with the relationship of computation and biology, which in addition to biologically inspired computing also comprises of computationally motivated biology and computing with biology. As suggested by the names of these sub-fields, computational biology is investigation of biology with computation such as simulations, artificial life, and synthetic biology, whereas computation with biology is the exploitation of the computational abilities of natural systems such as DNA-computing, and soap-bubbles which can solve NP-complete problems [28,66,75].

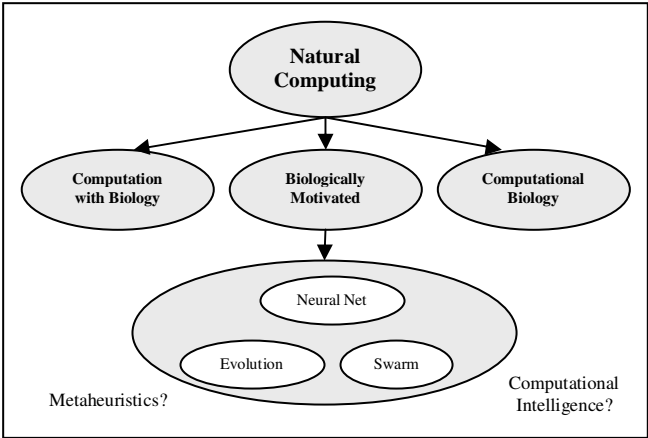


Figure 2 - Depiction of natural computation and the relationship of biological motivation to computational intelligence

Thus, the field of artificial intelligence, specifically the scruffy variety (computational intelligence) motivates the work from the perspective of an intelligent problem-solving strategy in computer science, whereas the field of natural computing, specifically the biological inspired computation variety motivates the actual form and information processing capabilities of the strategy.

B. The Specific Field

The limit of biological inspirations is as abundant as there are biological systems, and more importantly perspectives on biological systems. Given that the concern is principle mechanisms of intelligent information processing, many motivations come from theoretical sub-disciplines of biology and sociology.

General	Examples	Biological Motivation
Evolutionary	Genetic algorithms	Evolutionary theory
Evolutionary	Artificial immune systems	Immunological theory
Swarm	Ant colony optimisation	Ant foraging and communication theory
Swarm	Particle swarm optimisation	Fish and bird flocking theory
Connectionist	Neural networks	Neural science theory

Table 1 - Example of some general computational paradigms, specific examples and their biological motivation

Artificial Immune Systems (AIS) is a sub-field computational intelligence motivated by immunology (primarily mammalian immunology) that emerged in the early 1990's (for example [30,90]), based on the *proposal* in the late 1980's (such as [26,32]) of applying theoretical immunological models to machine learning and automated problem solving. The early works in the field were evolved from exotic theoretical models (immune network theory) and were applied to machine learning, control and optimization problems. The approaches were reminiscent of paradigms such as neural network, genetic algorithms, reinforcement learning, and classifier systems. Perhaps the most formative works in the field were those that proposed the immune system as an analogy for information protection systems in the field of computer security. Examples include the Computer Immunity [77,80] and Immune Anti-Virus [36,37]. These works were formative because they provided a natural and intuitive application domain that captivated a broader audience and assisted in differentiating the work as an independent subfield (see [52] for a terse summary of the history of the field).

Why use the immune system to motivate computational intelligence?

The motivation for the field of AIS is the immune system, specifically architecture, components, principles and theories used to explain observed function. The mammalian immune system provided a basis given the extent to which the system has been studied, and specifically aspects of the system as they relate to acquired immunity – a biological feature unique to jawed vertebrates in which the host system can adapt a defensive strategy through interactions with an environment. The authors de Castro and Timmis defend the immune system as an inspiration for computational intelligence by providing a comprehensive listing of abstracted information processing principles [52] (pages 55-56). This list in summary includes: *pattern recognition, uniqueness, self identity, diversity, disposability, autonomy, multilayered, no secure layer, anomaly detection, dynamically changing coverage, distributability, noise tolerance, resilience, fault tolerance, robustness, immune learning and memory, predator-prey pattern of response, self-organisation, and integration with other systems*. Forrest and Hofmeyr take a similar approach in considering and abstracting the information processing principles of the immune system [78]. Although in that work the authors focus on three specific information-processing principles, they highlight a number of general design principles that have much overlap with the de Castro-Timmis listing. This list in summary includes *diversity, distributed, error tolerant, dynamic, self-protecting, and adaptable*.

Perhaps the more important features that strongly entrench the field of computational intelligence are immune learning (acquired information through interaction with the environment) and immune memory (persistence and ongoing application of acquired information for short and long durations), both of which fit into a broad notion of intelligence. Thus, *the mammalian acquired immune system may be considered rudimentary intelligent*.

What is an Artificial Immune System?

The same authors provide a considered definition of an artificial immune system, taking into considerations the problem solving intentions of the computational models, distinct from those theoretical immunological models that simulate immune function.

Definition: Artificial immune systems (AIS) are adaptive systems, inspired by theoretical immunology and observed immune functions, principles and models, which are applied to problem solving

Figure 3 - Definition of an artificial immune system ([52], page 58)

The definition is clarified such that attributing immunological terminology is insufficient to call a system an artificial immune system. Specifically, a system must incorporate a minimum level of immunology, such as an immune component (for example cell, molecule, and organ), it has to be designed by incorporating ideas from theoretical and or experimental immunology, and it has to be directed toward problem solving.

C. The Specific Problem

The specific problem in the field of artificial immune systems is the investigation of systems that are motivated by the distributed information processing principles of the acquired immune system. Interested in considering the information processing of the acquired immune system in a the broader context of the host organism (holistic perspective).

Problem: *Investigated into artificial immune systems motivated by the distributed information processing of the acquired immune system*

This problem was considered with regard to three different, yet related methodologies.

- 1) *Immunology Information Processing*
- 2) *Conceptual Framework*
- 3) *Investigating Conceptual Machines*

The first methodology was proposed by Forrest and Hofmeyr [78] in the work by Segel and Cohen on the design principles for the immune system as a distributed autonomous system [54]. In this book chapter, the authors consider the immune system as the basis for information processing. They propose a methodological process for identifying and exploring information processing artefacts from immunology in the context of computer science called '*immunology information processing*'. The proposed process is simple and intuitive in the context of the field of biological inspired computation. Step one of the process is presupposed as '*distributed information processing*', although this general principle was decomposes into a number of '*identified mechanisms*', each of which became the focus of the process.

Immunology as Information Processing

- 1) Identify a specific mechanism that appears to be interesting computationally
- 2) Write a computer program that implements or models the mechanism
- 3) Study its properties through simulation and mathematical analysis
- 4) Demonstrate its capabilities either by applying the model to a biological question of interest or by showing how it can be used profitably in a computer

Figure 4 - Summary of the Immunology Information Processing methodology (from [78])

The immunology information processing methodology was selected because it provides a good high-level process for selecting, modelling, analysing, and verifying distributed information processing mechanisms from the acquired immune system. The methodology lacks detail and structure for the analysis process. The '*conceptual framework*' structures the transition from 'identified mechanism' to abstraction, framework, and ultimately algorithm, complementing the immunology information processing methodology by adding the required detail [34,85,86]. In [86], Stepney, et al. caution that in following a process that lacks detail in their 'modelling' step (abstraction and framework), that one may fall into the trap of 'reasoning by metaphor'. Besides the lack of rigor, the trap suggests that such reasoning and lack of objective analysis limits the suitability and applicability of resultant algorithms, and propose that many algorithms in the field of AIS have succumbed to this trap. Like the immunology information processing methodology, the conceptual framework provides a general process that may be applied generally in the field of biological inspired computation toward realising biological inspired computational intelligence systems.

Conceptual Framework for Biological Inspired Algorithms

Biological System: The driving motivation for the work that possess some innate information processing qualities

Probes: Observations and experiments that provide a partial or noisy perspective of the biological system

Models: From the probes we build and validate abstract and simplified models of the information processing qualities of the system

Framework: Build and validate analytical computational frameworks. Validation may use mathematical analysis, benchmark problems and engineering demonstration

Algorithms: The frameworks provide the principles for designing and analysing algorithms that may be general and applicable to domains unrelated to the biological motivation

Figure 5 - Summary of the conceptual framework for devising and investigating biological inspired algorithms (from [86])

The conceptual framework intuitively suggests that in identifying the mechanisms that underlying the acquired immune systems distributed information processing, one must raw upon probes (research from experimental and theoretical immunology), that must be distilled into their basic information processing qualities and verified before making the transition to computational intelligence algorithms and systems.

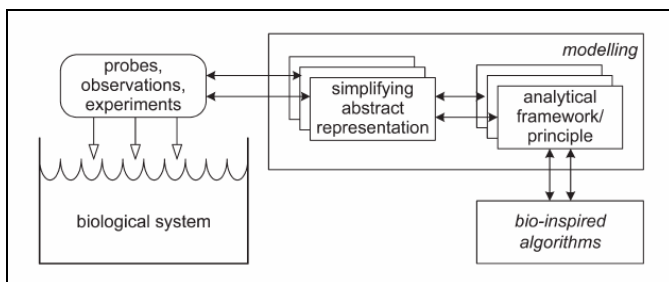


Figure 6 - Depiction of the conceptual framework for devising biological inspired algorithms (taken from [86])

The immunology information processing and conceptual framework together provide a structure process for investigating the proposed problem, although an important aspect not considered by either methodology is the level and type of analysis required. Like the problems represented by these two frameworks, the level of analysis is also a pervasive problem in the field of study. This problem has been pursued (perhaps ruthlessly) by Goldberg in his study of genetic algorithms (not limited to [15-19]) culminating in a book [20]. Goldberg proposes an 'economy of modelling' in which careful attention is paid to the fidelity of constructed models (effort to construct). He proposes an engineering-inspired methodology for investigating what he refers to as '*conceptual machines*' where 'small models' are the dominant model used for analysis. Specifically facet-wise models (simple mathematical investigations of decomposed mechanisms), and dimensional analysis (analysis of models of scale) are used, and integrated in a patch-quilt manner to give an overall analysis of a problem. Qualitative (lower cost empirical observations) models are used when such analysis is unavailable, and descriptions of motion (higher cost mathematical analyses) are used when time permits). Goldberg suggests that such an economy of model provides rigorous analysis of complex problems in a timely manner, providing a required analytical methodology to complement the information processing and conceptual framework processes.

'Small Models' Methodology Summary

- 1) Decompose the large problem approximately and intuitively, breaking into quasi-separate sub-problems
- 2) Investigate each sub problem separately (or as separate as possible) using empirical testing coupled with adequately predictive, low-cost models
- 3) Assemble the sub-solutions and test the overall invention, paying attention to unforeseen interactions between the sub-problems

Figure 7 - Summary of the methodology from [17], inspired by an assessment of the Wright brothers in [25]

The general problem to be investigated was selected for number of reasons that may be reduced to the following listing:

- 1) The 'distributed' information processing principles of the immune system are frequently identified and highlighted in the AIS literature (for example [4,7,44])
- 2) Given (1), there are few (if any) studies that target the distributed principles, particularly with regard to the structured investigation (see the survey in [52], highlighted in [7,10])
- 3) Given (2), there are few (if any) frameworks in which to consider distributed information processing models and algorithms (most popular is cell-focused called immune engineering framework [52], two approaches at encouraging distributed frameworks [53,91])
- 4) The field of artificial immune systems has reached an impasse (for example [40]), such that attention to existent models is increasingly critical ([76]), seeking new metaphors to base AIS (for example non-human [33], cognitive [70], innate [34])

III.BACKGROUND

This section provides a summary of the field of

artificial immune systems from the perspective of cell-based immunological theory and the abstracted information processing, algorithms and applications that the theories have inspired. This section also discusses some mechanisms that may underlie the distributed information processing qualities of the acquired immune system. These mechanisms are suggested firstly after providing a physiological context for the cell-based theories, and secondly by providing extended the context from that of a single host with an immune system to a population of such hosts, whose immune systems interact.

A. Cell-Based Artificial Immune Systems

This section provides a summary of the field of artificial immune systems from the perspective of immunological theory of immune cell interactions, the abstracted information processing principles, and the algorithms and applications that have been proposed. This taxonomy consists of three primary areas: clonal selection, negative selection, and immune network. In addition, other emergent theoretical bases for AIS are summarised, as are the few works that consider the distributed properties of the acquired immune system.

Clonal Selection

The acquired immune system produces antibodies (molecules) that can bind to and neutralise molecules, and microorganisms (antigen – things that elicit an immune response) that infiltrate the host organism. The interesting thing is that the system responds better to subsequent exposures, both in terms of the speed of the response and the specificity (ability to detect). Further, the system is capable of raising antibodies to synthetic substances that have never existed in nature. Thus, the system cannot have prior knowledge of the antigens it will have to respond to (constructionist side chain theory), and given the genetic nature of antibody proteins the system cannot use antigens as templates (instructions template theory [55]). The clonal selection theory credited to Burnet [22,23], based on Jerne's natural selection theory [59] accounts for the behaviour and capabilities of antibodies in the acquired immune system. Inspired by the principles of Darwinian natural selection (theory of evolution), the theory proposes that antigen select-for immune cells (lymphocytes) that have antibody bound to their surface. Binding to the antigen, the lymphocytes proliferate (making many thousands more copies), and differentiate into different cell types, one type that produces vast quantise of antibody molecules (plasma cells) and another that stays around for a long time (memory cells). The important feature of the theory is that when the selected cell is selected and proliferates, it is subjected to small copying errors (changes to the genome called hypermutation) the affect the antibodies on the cells surface, and the antibodies that plasma cells produce.

This theory is very interesting from an information processing perspective. It suggests that an initial repertoire of general immune cells, the system is able to change itself (the compositions and densities of cells) in response to the environment. Through a blind process of selection and accumulated variation (on the large scale

of many billions of cells), it is capable of acquiring the necessary information to protect the host organism from the specific pathogenic dangers of the environment. It also suggests that the system must guess (anticipate) at the pathogen to which it will be exposed, and requires exposure to pathogen (which may harm the host) before it can acquire the necessary information to provide a defence.

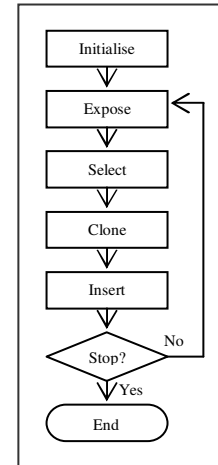


Figure 8 - Algorithmic description of a general clonal selection algorithm

The information processing principles of the clonal selection theory describe a general learning strategy. The theory has inspired a plethora of algorithms for optimization, classification, and other rudimentary machine learning problem domains. In each algorithm, a population of adaptive information units (each representing a problem-solution or component thereof) is subjected to processes of competition for selection, and resultant duplication and variation, that ultimate improves the information units, and solves or approximately solves a problem. The seminal algorithm was proposed by de Castro called the Clonal Selection Algorithm (CLONALG) [46,49] and was applied to function optimization, the travelling salesman problem and pattern recognition. Other optimisation algorithms include the B-cell algorithm (BCA) [38,39], and the multi-objective immune system algorithm (MISA) [13,65]. A popular classification algorithm inspired by the theory is the artificial immune recognition system (AIRS) by Watkins [5,6,8,9].

Negative Selection

An important consideration for Burnet (and others) in developing the clonal selection theory was integration of the fact that such a powerfully descriptive process does not immediately turn against the host organism in the generation of self-antibodies (autoimmune response). This ability of the clonal response to mature cells for pathogen and not self-tissues became known as 'self-nonself discrimination' [21,24]. Clonal selection accounted for this observation by proposing both that (1) the initial repertoire of immune cells were prepared in such a way that none were autoimmune, and (2) that during the maturation process of ongoing interaction with antigen that autoimmune variants are destroyed. Immune cells are continually being destroyed, thus there is a constant stream of new immune cells that must be created and integrated into the repertoire. Thus, the

negative selection of self-reactive naïve immune cells is an ongoing process. This was confirmed by the discovery of T lymphocyte cells (identify and neutralise infected cells) that are created and released from the thymus (an immune organ).

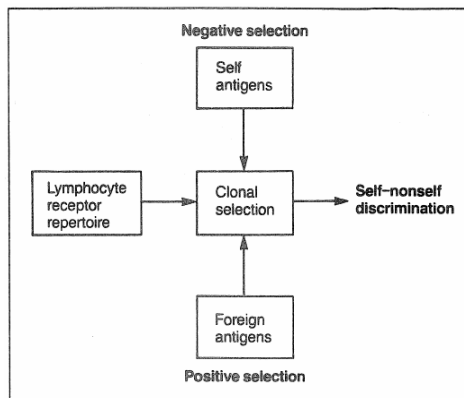


Figure 9 - Summary of clonal selection theory with integrated positive and negative selection (taken from [31], page 491)

The negative selection theory and self-nonself discrimination have interesting information processing properties. The theory suggests that the anticipatory guesses made in clonal selection are filtered by regions of infeasibility (protein conformation that bind to self-tissues). Further, the self-nonself immunological paradigm proposes the modelling of the unknown domain by modelling the complement of what is known. This is an unintuitive model, because the natural inclination is to model the unknown by what is different from what is known rather than guessing the unknown and filtering guesses by what is known.

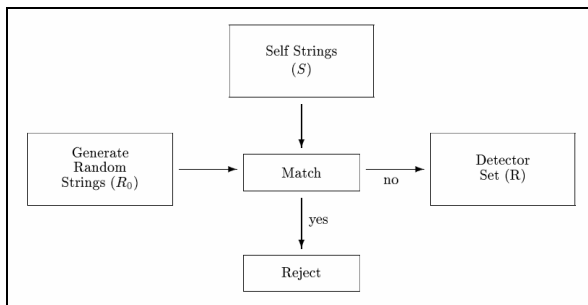


Figure 10 - Depiction of the detector generation process of the negative selection algorithm (taken from [77])

The information processing principles of the negative selection theory, specifically the self-nonself discrimination paradigm are that of an anomaly or change detection system that models the question of unknown anomalies or changes in the complement space (anticipates them). The seminal negative selection algorithm was proposed by Forrest, et al. [77] in which a population of adaptive units are prepared in the presence of known information (proposed units that match known data are discarded). The population of proposed guesses at the unknown space then monitors the known information for changes. The algorithm was applied to the monitoring of files for changes (infections by viruses). The algorithm was formalised as a change detection algorithm [67,68]. It was applied to monitor changes in the execution behaviour of UNIX processes

[79,81], and to monitor the changes in TCP connections of a network computer (intrusion detection) [82,83]. The application of the algorithm has been predominantly to virus detection, host intrusion and their abstracted problems of classification (two-class) and anomaly (novelty, change) detection.

Immune Network

A concern of the clonal selection theory is that it presumes that the repertoire of reactive cells remains idle while not in use (when there are no antigen to which to respond). Jerne's immune network theory (idiotypic networks) proposes that immune cells are not at rest in the absence of antigen, instead that antibody and immune cells can recognise and respond to each other [60-62]. The theory proposes that antibody (both free floating and surface bound proteins) possess idiotopes to which other receptors can bind. The result of receptors interacting with each other is a dynamic repertoire where receptors continually both inhibit and excite each other providing regulatory networks (chains of receptors). Thus, clonal selection may be triggered by the idiotopes of other immune cells and molecules, and the maturation of the process applies both to the receptors themselves the idiotopes which they expose.

Clearly, the immune network theory has interesting resource maintenance and signalling information-processing properties. The clonal selection and negative selection theories integrate the accumulative and filtered learning of the acquired immune system, whereas the immune network theory proposes an additional order of complexity between the cells and molecules under selection. In addition to cells that interact directly with antigen, there are cells that interact with those reactive cells and with antigen indirectly, in successive layers such that networks of activity for higher-order structures such as internal images of antigen (promotion), and regulatory networks.

Early works, such as Farmer, et al. [32] (and others) suggested at the exploitation of the information processing properties of network theory for machine learning. The seminal network theory based algorithm was proposed by Timmis, et al. called the Artificial Immune Network (AIN) [43] (later extended and renamed RLAI [41,42] and AINE [87]). The algorithm maintains a population of adaptive units that operate under a clonal selection process. Units are connected to each other based in distance in the information space (for example Euclidean in the units are real-valued vectors), such that adaptive units that are 'close' in the information space suppress the activation of each other. Thus, the more 'connections' a given unit has with other nodes influences the units potential for being selected and cloned under clonal selection. The was applied to feature extraction and data clustering. Another seminal network based algorithm by de Castro and Von Zuben called aiNet (Artificial Immune Network) [47,48] which extended the principles of AIN and CLONALG and was applied to clustering. The aiNet algorithm was further extended to optimization domains and renamed opt-aiNet [51].

B. Distributed Mechanisms of the Immune System

The immune system is a collection of specialised organs, tissues, cells, and molecules for protecting a host organism from attack by microorganisms (pathogen), cancers, and other molecules (antigen) that find their way into the body. If the immune system specifically selects for, identifies, and neutralises a given pathogen, the host is said to be immune. Broadly speaking, the mammalian immune system may be partitioned into two layers of protection: the innate immune system and the acquired immune system. The innate system consists of physical barriers to limit the pathogen arrival within the host, in addition to rapid and specific defensive capabilities that evolve with the organism over evolutionary time. The acquired immune system provides a general defensive capability, which changes with exposures to provide a specialised defence for a given host. The field of Artificial Immune Systems is predominantly concerned with the adaptive immune system, and specifically with information processing models and algorithms based on the interaction between cells with antigen and with each other. Given the problem of distributed information processing, one may consider the context for the cell-based theories that dominate the contributions of AIS to computational intelligence. The context provides two principle considerations for basal mechanisms: (1) the spatial arrangement (physiology) of the acquired immune system, and (2) the mobility of the cells of the acquired immune system.

The organs and tissues responsible for the creation and maintenance of the cells of the acquired immune system known as the lymphoid organs, collectively referred to as the lymphatic system [1,56]. There are two types of lymphoid organs (1) the central or primary tissues which are the sites of *lymphocyte formation* (the thymus and bone marrow), and (2) the secondary or periphery lymphoid organs *where immune response takes place* (the spleen, lymph nodes and gut-associated lymphoid tissues). One may consider the rest of the body's tissues as tertiary lymphoid tissues which normally only contain few lymphoid cells, although on infection and inflammation, manage to recruit many immune cells.

"The central function of secondary lymphoid tissues is filtering: collecting blood-borne, lymph-borne, or mucus membrane antigens and holding these so that they can be surveyed by immune cells before being destroyed." ([12], page 6).

Perhaps more interesting with respect to the interaction between immune cells and antigen are the secondary lymphoid tissues. There are tissues that provide specialised filters to capture pathogen in mucus membranes entering the host, such as the tonsils and adenoids that guard the respiratory system, and the Appendix and Peyer's patches that guard the digestive system. There are tissues that provide specialised filters to capture pathogen circulating in blood, such as the spleen. Finally, there is the system of lymph nodes that provide collecting and filtering points for lymph (the fluid that permeates all tissues) that drains from non-lymphoid tissues. Each of these specialised tissues is

responsible for collecting antigen and facilitating its interaction with and potential response by immune cells (such as B and T lymphocytes).

"Nature's solution [...] has been to compartmentalize the principle functions of the lymphoid system into discrete organs and tissues in the body, and to connect and unify these organs through the operation of an elegant system of targeted lymphocyte trafficking and recirculation." ([45], page 562)

The immune cells that are the central focus of the clonal selection theory, the self-nonself paradigm and the network theory, and that are constantly exposed to pathogen in secondary lymphoid tissue generally do not have a static home, rather they move around. Lymphocytes recirculate around the host organism, using the vascular system as a high-speed transit system between lymphoid tissues [1,3]. In fact, cell movement is the basis of immunology. It is required for physiological processes such as inflammation, differentiation, adhesion, and cell contact, and the maturation processes described by clonal selection cannot occur without cell mobility. Two important specialised types of cell trafficking are cell homing and cell recruitment. Homing refers to the directed (preferential tendency) of lymphocytes activated in a particular region of the body to return to that part of the body. A specific example is the homing of T lymphocyte cells to sites of infection, given 'education' by dendritic cells that migrate from the site of infection to secondary lymphoid tissues to 'get help' [58]. Recruitment is the exertion of influence by tissues to sequester recirculation cells, typically to a site of recent activity such as infection and inflammation.

Thus, in considering immune physiology, we have tissue 'compartments' that impose constraints on resident cell-based information processing such as formation, presentation, and regulation. Further, the physiology of the lymphatic system we have cell recirculation between compartments providing general dissemination and surveillance, in addition to specialised trafficking patterns such as the cell-influenced homing and tissue-influenced recruitment processes. The important abstraction from this example is that (1) a broader context provided a pathway to identifying some mechanisms for distributed information processing, and (2) specifically that the movement of immune cells (sharing between compartments or disparate points of exposure) is an essential principle of such mechanisms.

Considering this observation, one may raise the level of detail of the cell-based information processing from that of the physiology of the lymphatic system to that of a host organism in a population of similar, but distinct host organisms. Generally, immunization implies that a host has been exposed to an antigen (immunogen) inducing an immune response that has educated the system with respect to more effectively and efficiently detecting and neutralising the antigen in the future. When a pathogen enters the host and elicits a response (and the host survives), the host gains a level of immunity to that pathogen. This process can be induced artificially through inoculation (controlled exposure to the pathogen), and is the basis of vaccination.

Interestingly, immunity is not limited to this reactive method, and evolution has designed a temporary and passive form of immunity that is employed by mothers to protect children before and after birth, which too, can be replicated artificially by the transplantation of mature cells between hosts.

	Natural	Artificial
Active Immunity	Infection	Vaccination, Inoculation
Passive Immunity	Maternal Immunity	Injection of antibodies

Table 2 - Summary of artificial and natural active and passive immunity

Passive immunity is the transfer of active humoral immunity in the form of ready-made antibodies to a host organism. Antibodies are relatively short-lived molecules that have no reproductive capability, thus the immunity provided is fast, effective, and temporally. Natural examples of this transfer of immunity include maternal immunity from mother to foetus during pregnancy called maternal immunity [88], and the transfer of antibodies from mother to child during breastfeeding called mucosal immunity [29]. Artificial examples include the injection of prepared antibodies to address viral and bacterial infections, as well as poisons such as snakebites [57]. Active immunity involves the stimulation of the system by an antigen and the development of an immune response. Natural active immunity is the normal function of the acquired immune system for neutralising pathogens. Artificial active immunity involves intentionally inducing the immune response by introducing an immunogen in a vaccine. A vaccine is typically administered before the patient contracts the disease, although may be administered after assuming the immune response to the immunogen is faster than the response to the infection. There are many different types of vaccines including inactivated (dead) pathogens, live attenuated (low virulence) pathogens, toxoids (inactive toxic compounds from pathogens), and subunit or pieces of pathogens. An aspect of population vaccination is an effect called ‘herd immunity’ [69,72,74]. This is where the majority of the population (perhaps more than 90%) is vaccinated for a disease, which provides protection for the entire population.

Thus, in considering artificial and natural varieties of conferring immunity to hosts an additional set of inter-host distributed information processing mechanisms are revealed. Specifically, the controlled and intentional exposure of hosts to pathogen (inoculation and vaccination), the transplantation and injection of acquired immune cells between hosts, and the conferring of acquired immunity from mother to foetus and child.

IV.A SYSTEM-ENVIRONMENT APPROACH

The clonal selection theory and the models and algorithms inspired by it and descendant theories are meaningless without a discussion of molecules that trigger **antibody generation** (*antigen*). Pathogens are antigens (typically living micro-organisms) that cause disease in a host, such as viruses and bacteria. This section conceptualises pathogens as external triggers stimulating an internal activation and response by an acquired immune system. This conceptualization is called a ‘*pathogenic exposure*’. It provides a much-needed perspective on the learning and memory qualities

of the acquired immune system. The system itself is embedded or situated in a ‘*pathogenic environment*’, to which it (generally) passively responds. Thus, a system has qualities of an intelligent agent (it is situated, intelligent, and acts autonomous), but does not act upon the environment other than with interact activations and responses.

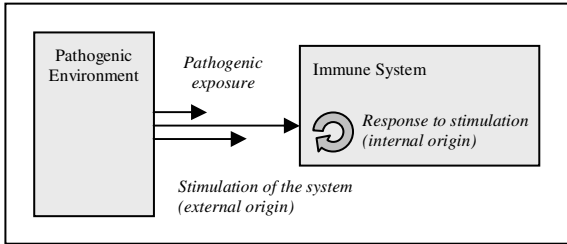


Figure 11 - Depiction of external stimulation resulting in internal activation

A consideration of pathogen is largely ignored in the investigation of artificial immune systems, as the investigatory concerns lie predominantly with the information processing qualities of the system (demonstrated with a discussion of the field in [52]). Although there are few if any works that explicitly use a system-pathogen conceptualisation from the ground up¹, there have been works that considered the environmentally situated nature of an artificial immune system, such as the context aware immune system [71].

A. The Pathogenic Exposure Paradigm

One may consider a bottom perspective the exposure paradigm. At the lowest level, a system is exposed to information patterns of external origin to which it must identify and respond. A given exposure has properties such as the (1) information content of the exposure, (2) the meaning of the information to the system, such as the exposures virulence, and (3) the quantity of information in the exposures that the information must consider. A pathogen exposure event may be extended to that of multiple exposures of a given pathogen. This adds a time component to the system, such that a system may or may not be subjected to an exposure. One may consider the additional pathogen properties of (1) the frequency of the exposure events over time where a system may have downtime, and (2) a general exposure regime that defines the behaviour (such as intent) of the pathogen over time. Finally, one may consider the paradigm further to that of multiple pathogens, a pathogenic environment. An environment consists of varied pathogen types, where each pathogen has its own exposure regime such that a given system may have to consider multiple concurrent exposures.

¹ To the authors knowledge

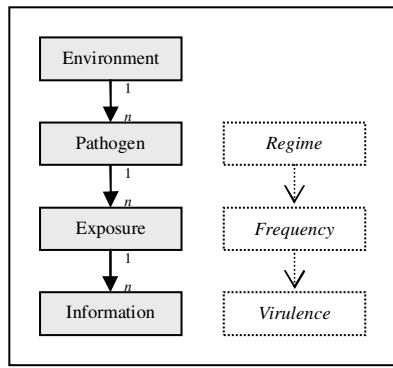


Figure 12 - Summary of the pathogenic paradigm

B. A Hierarchical Framework of the Immune System

The system-environment conceptualisation describes a classical *stimulus-response* relationship in which an immune system acquires information through pathogenic exposures in a broader pathogenic environment. The pathogenic exposure paradigm provides a broad conceptualisation of the unknown scope and delivery of information from the environment to the system. It has been demonstrated that the field of artificial immune systems is predominantly concerned with information processing at the cellular level. In considering the mechanisms that underlie any distributed information processing of the acquired immune system, a physiological cell mobility level was identified, and a population-based immunization level was identified. Fundamentally, the information processing at all three considered perspectives of the acquired immune system are based on the qualities of the pathogenic exposure paradigm and the clonal selection theory. Thus, a conceptual framework of the acquired immune system may be defined which is hierarchical and centred on the clonal selection principle. The three tiers of the framework are the cellular level concerned with cell interactions with pathogen and each other, the tissue level concerned with the lymphatic system and cell mobility, and the host level concerned with populations of hosts and host immunization.

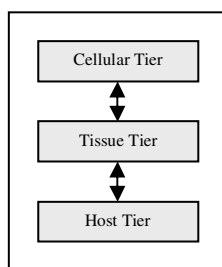


Figure 13 - Summary of the hierarchical acquired immune system framework

This framework unifies the identified distributed information processing mechanisms into a coherent abstraction that considers the same basic stimulus-response learning principles at three different scales of the acquired immune system.

V. MODELS ALGORITHMS AND FRAMEWORKS

Motivated by the identified immunological mechanisms and the hierarchical conceptual framework of the acquired immune system, this proposes

abstractions of the identified mechanisms, algorithms that embody the proposed abstractions, and a framework for verifying the proposed algorithms, as outlined in the conceptual framework biological inspired algorithm methodology.

A. The Cellular Level

The cellular level is rooted in the cellular based immunological theories, specifically clonal selection theory, and the extensions of negative selection, and immune network theory. Generally, this level of the framework is concerned with cells direct interactions with antigen and with other cells of the same or other types. This section provides four examples of information processing models that fit into this tier of the framework.

Clonal Selection Model

The first and obvious model at this level is that of clonal selection, based on the theory, and manifest in clonal selection algorithms. Existent algorithms (CLONALG, BCA, AIRS) are predominantly concerned with the optimization and classification capabilities of the algorithm. A broader perspectives may consider a collective of cells and the effect the selection and blind accumulation of variation has on this collective. A minimalist abstraction of the mechanism is manifest in the winner-take-all principle where the best information is selected and manipulated. The effect of the principle on the population is that of a parallel clonal dominance (hill climbing). The minimal model may be extended such the selected cells (winners) are subjected to clonal expansion, fostering changing cell densities in the population, and take-over of useful information proportional to its selection.

Methodology	System
Mechanism	The clonal selection theory of acquired immunity
Abstraction	The iterative exposure of information to a population of adaptive units that accumulate presented information.
Framework	Winner-take-all-principle, clonal dominance, clonal densities
Application	Optimization, Feature Detection, Pattern Recognition

Table 3 - Summary of the Clonal Selection Model

Spatial Clonal Selection Model

The clonal selection model may be extended such that a spatial population structure is employed. The effect of such a configuration is that the processes of selection expansion are constrained to an arbitrary spatial projection (such as a low dimensional lattice), which provides an abstraction of the spatial-temporal concerns of the clonal selection processes in dynamic germinal centres (where clonal selection occurs). The effect of this abstraction on the population is that spatial areas are implicitly assigned responsibility for antigen. Such responsibility results in a topological mapping that preserves the relationships between input signals in the spatial population structure.

Methodology	System
Mechanism	The germinal centre and the spatial organisation of cells in the undergoing clonal expansion
Abstraction	Clonal selection constrained by spatial population structure
Framework	Topological preservation, regional responsibility, spatial winner-take-all (dominance)
Application	Optimisation, Clustering, Feature Extraction

Table 4 - Summary of the Spatial Clonal Selection Model

Mediated Clonal Selection Model

A mechanism of cell interactions not discussed is that of the interaction between T and B lymphocytes. A class of T lymphocyte cells called 'helper T cells' are responsible for mediating the clonal response of B cells. When a B cell binds with antigen it becomes active, internalising the antigen and presenting chopped-up parts of it on the cells surface. Helper T cells recognise parts of antigen presented by B cells providing a secondary signal allowing the B cell to replicate and differentiate. The interaction between the cells provides a clonal selection mechanism for the helper T cells that in turn proliferate. This interaction mechanism is abstracted to a two-signal model. Two populations of cells are maintained, the first (B cells) provide feature detects for the input signals, which transform the signal and present it to the second population (T cells). The T cells treat activated B cells as input signals, responding by clonal expansion and in turn allowing the activated B cells that are recognised by the T cells to also clonally expand. The effect of the model is a model with decoupled feature detector and concept population. Concepts may be represented in the second population, which may be subjected to external feedback of their own (reinforcement). The effect is that the first population may selectively respond to input signals, remapping them, the combination of which may be interpreted by concepts in the second level. Such interpretation facilitates the construction of higher-order structures and meaning of the input signals, particularly in if bottom-up reinforcement is provided.

Methodology	System
<i>Mechanism</i>	The role of helper T cells in mediated which activated B cells may clonally expand (proliferate and differentiate)
<i>Abstraction</i>	Decoupled population of feature detectors (B cells) and aggregated concepts (T cells)
<i>Framework</i>	Higher-order structures, complex interactions, abstraction, Feedback
<i>Application</i>	Classification, Feature Extraction, Reinforcement Learning

Table 5 - Summary of the Mediated Clonal selection Model

Network Clonal Selection Algorithm

The final model is based on the network theory and the mechanism of inter-population cell interactions. The theory is abstracted as an extension of the clonal selection abstraction, where, like the mediated algorithm, those cells that are activated themselves become signals that may trigger activation. This is different from the existent network based approaches (such as AINE and aiNet) in that it is rooted in the population-based clonal selection model, rather than an ad hoc (spatial) network topological model. Unlike the mediated algorithm, activated cells become input signals that may activate other cells in the population. Like the mediated algorithm, each cell has two information patterns, the first is used for response-based matching, the second is used for activation-based matching, both of which are replicated and matured via clonal selection. The effect of this abstraction is that cell networks implicitly form within the population of cells. In addition to the triggering of cells by exogenous stimuli (antigen), the population is never at rest, constantly

responding to other activated cells. This activity is expected to provide a positive reinforcement and complex internal structures (regulation networks) for those cells that respond for pathogen.

Methodology	System
<i>Mechanism</i>	The immune network theory of B cell and antibody regulation
<i>Abstraction</i>	Pattern recognition between the cells of the population, those cells that are activated themselves become units for activation
<i>Framework</i>	Chains of activity, inhibition and reinforcement
<i>Application</i>	Reinforcement Learning, Cognitive Models

Table 6 - Summary of the Network Clonal Selection Algorithm

Summary

The information processing concerns of the models at the cellular level are concerned with responding to input signals and any other feedback. The general application areas include optimisation, pattern recognition, and classification much like the existing clonal selection algorithms. The more interesting are the mediated and network algorithms that implicitly facilitate the construction of internal models (more complex internal structures). Such structures provide opportunity for application domains such as reinforcement learning, function approximation, which although are still low-level information processing domains, require more complex internal models than the simple clonal selection model alone can provide.

B. The Tissue Level

The tissue level is rooted on the lymphatic system (primary, secondary, and tertiary tissues), and on the cell mobility between these tissues. Generally, this level of the framework is concerned with the information processing constraints imposed by the various tissues, and the interactions between the tissues in terms of the sharing of acquired information embodied as cells. As an abstraction, the information processing concerns of the system are those of multiple interfaces with an informational environment, and internal consistency of knowledge acquired from that environment. This section discusses tissue architectures and three cell mobility-based models.

Tissue Architectures

The lymphoid tissues and their responsibilities and constraints on cells and cell-interactions provide the mechanisms for a tissue based systems architecture. The abstraction of these tissue types is a graph structure where nodes represent information processing centres (for example one of the clonal selection models), which are connected (directed graph) to each other. Primary nodes are responsible for naïve cell creation such as positive and negative selection in the preparation of T lymphocytes. Naïve cells migrate to secondary tissues for possible interaction with pathogen and other cells. There are only very few primary tissues for a given system. Secondary nodes are responsible for the presentation of pathogen to naïve and mature cells. Secondary tissues are connected together via a high-speed cell migration pathway, an abstraction of the vascular system. Tertiary tissue nodes provide an interface with the environment, such that they provide an

entry point for pathogen that may or may not interact with cells, and which are streamed back to secondary lymphoid tissue for presentation.

There are two principle tissue-architecture configurations. The first is a filter model, with one primary and one or a small number of secondary tissues that filter a given pathogen entry point. This is an abstraction of the filtering properties of the spleen (filtering blood) and the tonsils and related (for filtering the repertory system). The second is a collection of such filter systems that are networked together via the high-speed pathway. This second configuration is an abstraction of the lymph node network and the filtering properties it has of the lymph. Finally, this last architecture provides the basis for cell mobility-based models of this level of the broader hierarchy.

Methodology	System
<i>Mechanism</i>	Responsibilities and constraints on cells and their interactions imposed by different lymphoid tissue types
<i>Abstraction</i>	A directed graph structure where nodes represent information processing centres, and connection represent cell trafficking pathways
<i>Framework</i>	Delegated responsibility, general information processing architecture, machine learning
<i>Application</i>	A basis for tissue-level models

Table 7 - Summary of the Tissue Architecture

Cell Recirculation Model

The recirculation of lymphocytes provides a mechanism that underlies the principle distributed information-processing property of the immune system. The abstraction of this mechanism involves a directed graph of information processing nodes (the lymph node architecture). Each node processes input signals from an information environment. A continuous process of lymphocyte trafficking occurs in a directed manner around the network (a pool or ring structure). A small sample of cells from each node is removed, transmitted to the neighbouring node, where it is integrated. This abstraction provides a model that provides multiple perspectives on a problem domain, which are exploited at a given information-processing node, and integrated into the larger model through sharing of a random sampling of acquired information. Thus, a given sufficient time for integration, the system provides a consistent representation of the information environment through sampling from multiple and likely different perspectives.

Methodology	System
<i>Mechanism</i>	The recirculation of lymphocytes in the blood between secondary lymphoid tissues of a host organism
<i>Abstraction</i>	Graph structure with unidirectional movement, each node provides an interface into the environment
<i>Framework</i>	Multiple perspectives, integration, exploitation, consistent response, information sharing, consensus
<i>Application</i>	Parallel optimisation, parallel classification, multiple objective optimisation

Table 8 - Summary of the Cell Recirculation Model

Cell Homing Model

A mechanism of cell mobility is a homing effect where cells selecting recirculate to tissues where that are useful. An example of this mechanism is the sampling properties of dendritic cells, which carry pathogen back

to secondary tissues where it can be presented. T cells interact with the presented pathogen, proliferate, and are imprinted with the location of the infection. This mechanism is abstracted to that of cells being imprinted with information in the graph tissue architecture as to where they are useful. When a cell is created from proliferation, it is imprinted with the tissue location. The movement process is thus adjusted to take this 'cell preference' into account when selecting which cells to recirculate. The effect of this imprinting and selective recirculation is that although all cells are subjected to movement, they exhibit a probabilistic preferentially residence in locations where they have been demonstrated to be useful. This results in information dissemination via recirculation, as well as information exploitation at locations where it is known to be useful. From a problem perspective, the system exhibits a spatial self-organisation of information to locations where the system anticipates it may be useful, although generally anticipates that the information may be needed across all points of contact.

Methodology	System
<i>Mechanism</i>	The education of lymphocytes as to the location in the host where they are needed, such as the education of T cells by dendritic cells
<i>Abstraction</i>	Preferential residence in the context of the recirculation model, cells return to the location of their application and creation
<i>Framework</i>	Spatial organisation, exploitation-integration
<i>Application</i>	Dynamic resource allocation, dynamic learning (optimisation, classification)

Table 9 - Summary of the Cell Homing Model

Cell Recruitment Model

A final interesting mechanism of cell mobility is the inflammation of tissues when they are infected with pathogen. Inflammation results in a swelling at the site and the increase in the number of immune cells at the site to address the pathogen concern. The inflammation mechanism is abstracted to that of cell recruitment in the tissue architecture, where information or novel information arrival is a random spatial-temporal event, thus resources must be applied if and when, and where such event occurs. The cell recirculation mechanism is modified to take into consideration whether a tissue is 'infected' recently and continually receiving information signals. If so, less cells are migrated away from the tissue (down stream), and more cells are migrated to the tissue (up stream). The effect is a decentralised and distributed recruitment mechanism in which the carrying capacity, and resources applied to a given exposure is changed in response to the availability of external information signals. The 'inflammation' effect further enhances the spatial self-organisation (anticipation) behaviours of the whole system.

Methodology	System
<i>Mechanism</i>	The inflammation and recruitment (sequestration) of recirculating lymphocytes by tissues at the site of infection
<i>Abstraction</i>	Inflammation of nodes in the context of the recirculation model
<i>Framework</i>	Distributed recruitment, spatial organisation
<i>Application</i>	Resource Allocation, dynamic learning

Table 10 - Summary of the Cell Recruitment Model

Summary

The general information processing concerns of tissue-level models is the exploitation of multiple perspectives on an information environment, and the integration of the information into a cohesive whole. This behaviour may be enhanced by subtle adjustments of the decentralised (local) recirculation process such as in the case of homing and recruitment, fostering the self-organising of information into a spatial-anticipation model. Although distributed, the ring-based constraint of recirculation suggests application on a single machine or small network. This was the approach taken in a learning environment proposed by these models called IIDLE [35]. Applications included the exploitation and integration of multiple problem constraints (multiple objectives) and multiple information processing mechanisms (hybrid search).

C. The Host Level

The host level of the framework is rooted in a population-based consideration of the acquired immune system. Specifically the population-based manipulation of acquired immunity via artificial-and-natural, passive-and-active immunization. The general concerns of models at this level are the sharing of environment information and acquired information between entire systems in an ad hoc population-based manner. This section discusses two population-based models, and two generation-based models.

System Population Architecture

A population of organisms with acquired immune systems is abstracted to an system population architecture. Systems live for a time in the information environment and new systems may enter and leave the environment. Each system as a number of perspectives on its local environment, such as an example of one of the tissue models. Systems may transfer information to other systems in their local vicinity, thus inter-system interaction is localised, and ad hoc, unlike the structured interaction between nodes in models of the tissue level. Each system in the population is distinct, providing a set of unique and robust perspectives on the information environment.

Methodology	System
<i>Mechanism</i>	Population of organisms with acquired immune systems
<i>Abstraction</i>	Population of systems with local and unstructured interactions
<i>Framework</i>	Peer-to-peer, multiple system perspectives
<i>Application</i>	A basis for population-based models

Table 11 - Summary of the System Population Architecture

System Vaccination Model

Vaccination provides a mechanism for the interaction between systems, where an immunogen for a given disease is administered to large portions of the population to protect against the disease (artificial active immunity). This may be abstracted to the population architecture, in which one system collects common and useful information from the environment and transmits it to much of the population. The systems that perform the vaccination are responsible for the identification of what information to transmit to other systems, which other systems to transmit it to, and when to do so. The effect is the localised collection and propagation of useful

information through the population mediated by the unstructured localised interactions between systems. The vaccination effect provides a controlled alternative to the environment for systems being exposed to information.

Methodology	System
<i>Mechanism</i>	The controlled exposure of immunogen to systems as in vaccination or inoculation (artificial active)
<i>Abstraction</i>	Selective exposure to other systems of information which may or may not be acquired by the other systems
<i>Framework</i>	Information dissemination, propagation
<i>Application</i>	Peer-to-peer, recommender

Table 12 - Summary of the Vaccination Model

Shared Immunity Model

Acquired immunity may be administered such as antibodies in the case of snake anti-venom, and in the transplantation of immune cells. This mechanism is referred to as artificial passive immunity. This may be abstracted in the context of the population model where information acquired by a given immune system may be transmitted to another system in the local vicinity. The difference between the shared immunity model and the vaccination model, is that this model concerns the restricted transmission of acquired information, whereas the vaccination model involves the broader transmission of environmental information to which each system must respond (or not respond) in their own way. The effect of this model is the localised propagation of acquired information, which although becomes integrated in other systems, is likely to have a short lifespan in the receiving system unless it is put to direct application.

Methodology	System
<i>Mechanism</i>	The transplantation of acquired immunity between hosts in a population (artificial passive)
<i>Abstraction</i>	Selective transmission of acquired information between systems in the population
<i>Framework</i>	Dissemination, consistency, propagation, short term
<i>Application</i>	Peer-to-peer, recommendation

Table 13 - Summary of the Shared Immunity Model

System Generational Architecture

A population of organisms with acquired immune systems interact to reproduce and continue the population. This simple augmentation to the population architecture may be abstracted to a generational system population architecture where naïve systems are introduced into the information environment, and mature systems may be removed from the information environment. Such a consideration, takes into account ad hoc addition and removal of entire systems to a general problem environment, and provides a basis for generational-based population models. In this architecture, a given system is allocated an extended period of time in which to interact with the information environment before being removed from the system and replaced with a naïve system.

Methodology	System
<i>Mechanism</i>	Reproduction of organisms with acquired immune systems
<i>Abstraction</i>	Generational population structure such that mature systems die, and naïve cells are created h
<i>Framework</i>	Peer-to-peer, multiple perspectives, restart on perspectives
<i>Application</i>	A basis for generational-based models

Table 14 - Summary of the System Generational Architecture

Maternal Immunity Model

Maternal immunity is the passive transfer of acquired immunity from mother to foetus across the placenta, and from mother to child in breast milk (mucosal immunity). The new organism has a naïve immune system with regard to the environment, and the transfer of acquired immunity provides a boost to the infant increase survival in the early stages of life. This may be abstracted to a the generational architecture in which newly created naïve systems are provided with a sample of acquired immunity from one (or a small number) of systems in the population. As in the case of shared immunity, the received acquired information is likely to provide a rapid boost in information only if that information is presently useful, otherwise, attrition and localised adaptation will result in loss. A careful balance of is needed in the transmitted information. Too much information will in essence make the child a clone of the mature system, loosing advantages of a distinct new perspective of the environment. The transmission of too little information means that any benefit that the naïve system may achieve with the information boost will be unlikely.

Methodology	System
Mechanism	The sharing of acquired immunity from mother referred to as maternal immunity, or via breast milk referred to as mucosal immunity
Abstraction	Seed new instantiations of systems with acquired information from more established systems
Framework	Generational propagation, sharing, short-term, boost
Application	Peer-to-peer, sensor network, recommend, navigation

Table 15 - Summary of the Maternal Immunity Model

Evolved Immunity Model

The ongoing reproduction of organisms is subjected to the processes of neo-Darwinian evolution. Much like the processes that govern the clonal selection theory, evolution is based on the proliferation of organisms differentiated by relative fitness, where the reproduction process is subjected to blind errors (mutations) which effect the basis for selection. This mechanism is abstracted in the context of the generational architecture such that evolution is applied to parameterised mechanisms that influence a given systems interaction with the environment. Evolved traits may include the process that generates a given system initial cell repertoire and the organisation and structure of tissues in a system. The effect of this model is that in addition to systems acquiring information from their interaction with their environment over their lifetime, from a population perspective, systems are acquiring information regarding the tools for useful interaction with their environment. This provides information acquisition at two different scales, both in time and in the nature of the information being acquired.

Methodology	System
Mechanism	The application of neo-Darwinian principles of evolution to the genetic basis of traits that influence acquired immunity over general time, such as the basis for the initial repertoire and system structure
Abstraction	Evolve the basis for acquiring information, traits
Framework	Interaction with the environment, adaptation, optimisation, continual improvement
Application	Evolution of adaptation, open system

Table 16 - Summary of the Evolved Immunity Model

Summary

The general information processing concerns of models in this level of the hierarchical framework is that of the interaction of whole systems in an information environment. Specifically, the interactions are focused on the sharing of identified information and of acquired information. Each system has multiple perspectives on its local information environment, and each system represents a cohesive perspective on the broader problem. As such, application may require each system to be implemented on its own machine, and interactions achieved through inter-machine communication such as networking. Example applications include computer security such as anti-virus and intrusion detection, as well as sensor networks.

VI.FRAMEWORK ELABORATION AND INTEGRATION

This section considers the system-environment framework again, in the context of the hierarchical framework of the acquired immune system and the models proposed for each level. This section discusses the common themes observed of the models through the hierarchy, and proposes some general open problems to which the models may be applicable. Finally, a general model is proposed as a framework for Artificial Immune Systems.

A. Common Themes

This section lists some common themes observed of the models across each of the three levels of the hierarchy framework.

- **Adaptation:** Models are concerned with adaptation from a distinct pseudo-random starting position to a system that effectively responds to a localised information environment. Adaptation includes the properties of learning and memory at various scales and speeds.
- **Redundancy:** At each of the three levels the information medium of the model is redundant. This redundancy is achieved through (1) duplication inherent in the clonal selection process, (2) the dissemination of copies throughout a broader architecture, and (3) the resultant effect of robustness to failure, loss, or corruption of individual and groups of information. The scale of the systems adjusted the level of redundancy (number of cells)
- **Autonomous:** The information processes are inherently autonomous, decentralised, and distributed, such that systems effects are emergent from the localised (unit-wise) decision making processes
- **Unit of Adaptation:** At each level, the cell is the medium of information and the unit of adaptation. The architectures provided more elaborated architectures and facilitated interactions.
- **Interaction:** Models interacted with internal components (endogenous), and or trigged by stimuli provided by the information environment (exogenous)

B. Cross-Framework Applications

Specific suitable engineering and computer science applications are not known for each model across the hierarchical framework. Instead, general domains are suggested based on the equally general emergent information processing behaviour and emergent effects of models. This section proposes a set of possible application domains that have the unique property of scaling with the scale information processing of the proposed framework.

	Cellular	Tissue	Host
<i>Remote Sensing</i>	Single sensor system	Multiple sensor network	Multiple network system
<i>Robot Navigation</i>	Single sensor robot	Multiple sensor robot	Multiple robot system (fleet)
<i>Fault Detection</i>	Single signal fault detection	Multiple signal fault detection	Multiple system fault detection (factory)
<i>Computer Security</i>	Single detection method	Multiple detection methods	Multiple systems (network)
<i>Anomaly Detection</i>	Single data stream	Multiple data streams	Multiple systems of feeds

Table 17 - Summary of general problem domains that scale with the information processing concerns of the hierarchal framework

C. General Model

The hierarchical framework of the acquired immune system may be equally matched with a hierarchical framework of the information environment. This equalling in scale of the information to which the adaptive systems respond provides symmetry to the framework

Level	System (acquired immune system)	Environment (pathogen)
<i>Cellular</i>	Tissue of cells	Infection of determinants
<i>Tissue</i>	Host of tissues	Habitat of infections
<i>Host</i>	Population of systems	Ecosystem of habitats

Table 18 - Summary of the symmetrical information processing system and environment

The proposed series of adaptive and distributed models represent the so called 'low hanging fruit' of the framework, what may be referred to as a horizontal perspective. Given the elaboration of the framework, and the clear one-to-many relationship between the layers, one may consider other perspectives of the framework as the basis for adaptive and distributed models. The following provides a listing of such perspectives:

- **Horizontal:** Traditional perspective, taken in the proposal of the series of adaptive and distributed models (cellular, tissue, host), so called 'low hanging fruit'
- **Vertical:** A perspective in which a given system considers the information processing concerns above and below the present level. A so-called 'pure' vertical model would be comprised of systems at the host level, each of which is comprised of a multiple tissue model, where each tissue model is comprised of a variety of the cellular models. Although this was the spirit of the models proposed at the horizontal perspective, a subsumed arrangement was not a constraint, merely

a guideline.

- **Irregular:** A perspective in which the information processing of one level (a model) is mixed with the information processing of another. Examples may include the embedding of clonal selection models at the host level, or the host-based communication between tissue models.

The hierarchical provides a clear and simple framework that is both unified in the relationship between the levels, and strongly tied to immunological theory. The simple models proposed only hint at the modelling and algorithmic possibilities the framework may provide in the field of artificial intelligence. Much work remains, not limited to the rigors verification of the proposed series of adaptive and distributed models, and the application of verified models to suitable engineering and computer science problem domains.

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REFERENCES

- [1] A. O. Anderson. Structure and organization of the lymphatic system. In: *Immunophysiology : the role of cells and cytokines in immunity and inflammation*, eds. Joost J. Oppenheim and Ethan M. Shevach. New York: Oxford University Press, 1990, pp. 14-45.
- [2] Aaron Sloman . Must intelligent systems be scruffy? In: *Evolving Knowledge in Natural Science and Artificial Intelligence*, eds. J E Tiles, G T McKee, and G C Dean. London : Pitman, 1990.
- [3] Alan J. Young, The physiology of lymphocyte migration through the single lymph node in vivo *Seminars in Immunology*, vol. 11, pp. 73-83, 1999.
- [4] Andrew B. Watkins, Exploiting Immunological Metaphors in the Development of Serial, Parallel, and Distributed Learning Algorithms 2005. University of Kent.
- [5] Andrew B. Watkins and Lois C. Boggess, "A Resource Limited Artificial Immune Classifier," *Proceedings of Congress on Evolutionary Computation*, HI, USA, pp. 926-931, May 2002.
- [6] Andrew Watkins and Jon Timmis, "Artificial Immune Recognition System (AIRS): Revisions and Refinements," *1st International Conference on Artificial Immune Systems (ICARIS2002)*, University of Kent at Canterbury, pp. 173-181, 2002.
- [7] Andrew Watkins and Jon Timmis, "Exploiting Parallelism Inherent in AIRS, an Artificial Immune Classifier," *Proceedings of the 3rd International Conference on Artificial Immune Systems (ICARIS2004)*, Catania, Sicily, Italy, pp. 427-438, 2004.
- [8] Andrew Watkins, Jon Timmis, and Lois Boggess, Artificial Immune Recognition System (AIRS): An Immune-Inspired Supervised Learning Algorithm *Genetic Programming and Evolvable Machines*, vol. 5, pp. 291-317, Sep, 2004.
- [9] Andrew Watkins and Lois Boggess, "A New Classifier Based on Resource Limited Artificial Immune Systems," *Proceedings of Congress on Evolutionary Computation*, Honolulu, USA, pp. 1546-1551, May 2002.
- [10] Andrew Watkins, Xintong Bi, and Amit Phadke, "Parallelizing an Immune-Inspired Algorithm for Efficient Pattern Recognition," *Intelligent Engineering Systems through Artificial Neural Networks: Smart Engineering System Design: Neural Networks*, pp. 225-230, 2003.
- [11] Andries P. Engelbrecht. *Computational Intelligence: An Introduction*, J. Wiley & Sons, 2002.
- [12] C. C. Goodnow, Chance encounters and organized rendezvous *Immunological Reviews*, vol. 156, pp. 5-10, 1997.
- [13] Carlos A. Coello Coello and Nareli Cruz Cortes, "An Approach to Solve Multiobjective Optimization Problems Based on an Artificial Immune System," *First International Conference on Artificial Immune Systems (ICARIS)*, University of Kent at Catenbury, UK, pp. 212-221, 2002.
- [14] Christian Blum and Andrea Roli, Metaheuristics in combinatorial optimization: Overview and conceptual comparison *ACM Computing Surveys (CSUR)*, vol. 35, pp. 268-308 , Sep, 2003.

- [15] David E. Goldberg, Making genetic algorithms fly: a lesson from the Wright brothers *Advanced Technology For Developers*, vol. 2, pp. 1-8, 1993.
- [16] David E. Goldberg, First Flights at Genetic-Algorithm Kitty Hawk pp. 71994.
- [17] David E. Goldberg, Toward a mechanics of conceptual machines: Developments in theoretical and applied mechanics *Proceedings of the Eighteenth Southeastern Conference on Theoretical and Applied Mechanics*, vol. pp. 1-9, 1996.
- [18] David E. Goldberg, The Race, the Hurdle, and the Sweet Spot: Lessons from Genetic Algorithms for the Automation of Design Innovation and Creativity. In: *Evolutionary Design by Computers*, ed. Peter J. Bentley. USA: Morgan Kaufmann, 1999.pp. 105
- [19] David E. Goldberg, The Design of Innovation - Lessons from Genetic Algorithms, Lessons for the Real World *Technological Forecasting and Social Change*, vol. 64, pp. 7-12, 2000.
- [20] David Edward Goldberg. *The Design of Innovation: Lessons from and for Competent Genetic Algorithms*, USA: Kluwer Academic Publishers, 2002.
- [21] Eileen Crist and Alfred I. Tauber, Selfhood, Immunity, and the Biological Imagination: The Thought of Frank Macfarlane Burnet *Biology and Philosophy*, vol. 15, pp. 509-533, Sep, 2000.
- [22] Frank Macfarlane Burnet, A modification of Jerne's theory of antibody production using the concept of clonal selection *Australian Journal of Science*, vol. 20, pp. 67-69, 1957.
- [23] Frank Macfarlane Burnet. *The clonal selection theory of acquired immunity*, Nashville, Tennessee, U.S.A.: Vanderbilt University Press, 1959.
- [24] G. J. V. Nossal, Negative Selection of Lymphocytes *Cell*, vol. 76, pp. 229-239, 1994.
- [25] G. L. Bradshaw and M. Lienert, The invention of the airplane *Proceedings of the Thirteenth Annual Conference of the Cognitive Science Society*, vol. pp. 605-610, 1991.
- [26] G. W. Hoffmann, A Neural Network Model Based on the Analogy with the Immune System *Journal of Theoretical Immunology*, vol. 122, pp. 33-67, Sep 7, 1986.
- [27] George F. Luger and William A. Stubblefield. *Artificial Intelligence: Structures and Strategies for Complex Problem Solving*, USA: Addison Wesley Longman Inc, 1997.
- [28] Gheorghe Paun, Bio-inspired Computing Paradigms (Natural Computing) *Unconventional Programming Paradigms*, vol. 3566, pp. 155-160, 2005.
- [29] Herbert B. Slade and Stanley A. Schwartz, Mucosal immunity: The immunology of breast milk *Journal of Allergy and Clinical Immunology*, vol. 80, pp. 348-358, Sep, 1987.
- [30] Hugues Bersini and Francisco Varela, "Hints for Adaptive Problem Solving Gleaned from Immune Networks," *Proceedings of the 1st Workshop on Parallel Problem Solving from Nature*, pp. 343-354, 1990.
- [31] Irun R. Cohen, The cognitive paradigm and the immunological homunculus *Immunology Today*, vol. 13, pp. 490-494, 1992.
- [32] J. D. Farmer, N. H. Packard, and Alan S. Perelson, The immune system, adaptation, and machine learning *Physica D*, vol. 22, pp. 187-204, 1986.
- [33] J. Twycross and U. Aickelin, "Biological Inspiration for Artificial Immune Systems," *Proceedings of the 6th International Conference on Artificial Immune Systems (ICARIS-2007)*, Santos/SP, Brazil, (In Press).
- [34] Jamie Twycross and Uwe Aickelin, "Towards a Conceptual Framework for Innate Immunity," *Proceedings ICARIS-2005, 4th International Conference on Artificial Immune Systems*, Banff, Canada, pp. 112-125, 2005.
- [35] Jason Brownlee, "IIDLE: An Immunological Inspired Distributed Learning Environment for Multiple Objective and Hybrid Optimisation," *Proceedings of the IEEE Congress in Evolutionary Computation (CEC'06)*, Sheraton Vancouver Wall Centre Hotel, Vancouver, BC, Canada, pp. 507-513, 2006.
- [36] Jeffrey O. Kephart, "A Biologically Inspired Immune System for Computers," *Proceedings of the Fourth International Workshop on Synthesis and Simulation of Living Systems*, pp. 130-139, 1994.
- [37] Jeffrey O. Kephart, Gregory B. Sorkin, William C. Arnold, David M. Chess, Gerald J. Tesauero, and Steve R. White, "Biologically inspired defences against computer viruses," *Proceedings of the 14th International Joint Conference on Artificial Intelligence (IJCAI '95)*, Montreal, Canada, pp. 985-996, 1995.
- [38] Johnny Kelsey, J. Timmis, and A. Hone, "Chasing chaos," *The 2003 Congress on Evolutionary Computation, (CEC '03)*, pp. 413-419, 2003.
- [39] Johnny Kelsey and Jon Timmis, "Immune Inspired Somatic Contiguous Hypermutation for Function Optimisation," *Proceedings, Part I Genetic and Evolutionary Computation Conference (GECCO 2003)*, Chicago, IL, USA, pp. 207-218, 2003.
- [40] Jon Timmis, Artificial immune systems - today and tomorrow *Natural Computing*, vol. 6, pp. 1-18, Mar, 2007.
- [41] Jon Timmis and Mark J. Neal, A resource limited artificial immune system for data analysis *Knowledge Based Systems Journal: Special Issue*, vol. 14, no. 3-4, pp. 121-130, 2001.
- [42] Jon Timmis and Mark Neal, "Investigating the evolution and stability of a resource limited artificial immune system," *Special Workshop on Artificial Immune Systems, Genetic and Evolutionary Computation Conference (GECCO) 2000*, Las Vegas, Nevada, U.S.A., pp. 40-41, 2000.
- [43] Jon Timmis, Mark Neal, and John Hunt, An Artificial Immune System for Data Analysis *Biosystems*, vol. 55, pp. 143-150, 2000.
- [44] Jon Timmis, Thomas Knight, Leandro N. de Castro, and Emma Hart. An Overview of Artificial Immune Systems. In: *Computation in Cells and Tissues: Perspectives and Tools for Thought*, Anonymous Springer, 2004.pp. 51-86.
- [45] L. J. Picker and E. C. Butcher, Physiological and Molecular Mechanisms of Lymphocyte Homing *Annual Review of Immunology*, vol. 10, pp. 561-591, 1992.
- [46] Leandro N. de Castro and Fernando J. Von Zuben, "The Clonal Selection Algorithm with Engineering Applications," *Proceedings of the Genetic and Evolutionary Computation Conference (GECCO '00), Workshop on Artificial Immune Systems and Their Applications*, Las Vegas, Nevada, USA, pp. 36-37, 2000.
- [47] Leandro N. de Castro and Fernando J. Von Zuben, "An evolutionary immune network for data clustering," *Proceedings Sixth Brazilian Symposium on Neural Networks*, Rio de Janeiro, RJ, Brazil, pp. 84-89, 2000.
- [48] Leandro N. de Castro and Fernando J. Von Zuben. Chapter XII: aiNet: An Artificial Immune Network for Data Analysis. In: *Data Mining: A Heuristic Approach*, eds. H. A. Abbass, R. A. Sarker, and C. S. Newton. USA: Idea Group Publishing, 2001.pp. 231-259.
- [49] Leandro N. de Castro and Fernando J. Von Zuben, Learning and optimization using the clonal selection principle *IEEE Transactions on Evolutionary Computation*, vol. 6, pp. 239-251, Jun, 2002.
- [50] Leandro N. de Castro and Fernando J. Von Zuben. Chapter 1: From Biologically Inspired Computing to Natural Computing. In: *Recent developments in biologically inspired computing*, eds. Leandro N de Castro and Fernando J. Von Zuben. Hershey, PA: Idea Group, 2005.
- [51] Leandro N. de Castro and Jon Timmis, "An artificial immune network for multimodal function optimization," *Proceedings of the 2002 Congress on Evolutionary Computation (CEC '02)*, Honolulu, HI, USA, pp. 699-704, 2002.
- [52] Leandro N. de Castro and Jon Timmis. *Artificial Immune Systems: A new computational intelligence approach*, Great Britain: Springer-Verlag, 2002.
- [53] Lee A. Segel, "The immune system as a prototype of autonomous decentralized systems," *IEEE International Conference on Systems, Man, and Cybernetics*, 1997. 'Computational Cybernetics and Simulation, Orlando, FL, USA, pp. 375-385, 1997.
- [54] Lee A. Segel and Irun R. Cohen. *Design Principles for the Immune System and Other Distributed Autonomous Systems*, USA: Oxford University Press, 2001.
- [55] Linus Pauling, A Theory of the Structure and Process of Formation of Antibodies *Journal of the American Chemical Society*, vol. 62, pp. 2643-2657, 1940.
- [56] M. A. Swartz, The physiology of the lymphatic system *Advanced drug delivery reviews*, vol. 50, pp. 3-20, 2001.
- [57] Margaret A. Keller and E. Richard Stiehm, Passive Immunity in Prevention and Treatment of Infectious Diseases *Clinical Microbiology Reviews*, vol. 13, pp. 602-614, 2000.
- [58] Marko Salmi and Sirpa Jalkanen, Lymphocyte homing to the gut: attraction, adhesion, and commitment *Immunological Reviews*, vol. 206, pp. 100-113, 2005.
- [59] N. K. Jerne, The natural-selection theory of antibody formation *Proceedings of the National Academy of Sciences of the United States of America*, vol. 41, pp. 849-857, 1955.

- [60] N. K. Jerne . Clonal selection in a lymphocyte network. In: *Cellular Selection and Regulation in the Immune Response* , ed. Gerald Maurice Edelman. 1974.pp. 39-48.
- [61] N. K. Jerne , Towards a network theory of the immune system *Annales d'immunologie (Annals of Immunology), Institut Pasteur (Paris, France), Societe Francaise d'Immunologie*, vol. 125, pp. 373-389, Jan, 1974.
- [62] N. K. Jerne , Idiotypic networks and other preconceived ideas *Immunological Reviews*, vol. 79, pp. 5-24, 1984.
- [63] Nancy Forbes , Biologically Inspired Computing *Computing in Science and Engineering*, vol. 2, pp. 83-87, 2000.
- [64] Nancy Forbes. *Imitation of life: how biology is inspiring computing*, Cambridge, Massachusetts: Mit Press, 2004.
- [65] Nareli Cruz Cortés and Carlos A. Coello Coello, "Multiobjective Optimization Using Ideas from the Clonal Selection Principle," *Proceedings, Part I Genetic and Evolutionary Computation Conference (GECCO 2003)*, Chicago, IL, USA, pp. 158-170, 2003.
- [66] P Marrow, Nature-Inspired Computing Technology and Applications *BT Technology Journal*, vol. 18, pp. 13-23, Oct, 2000.
- [67] Patrik D'haeseleer, "An immunological approach to change detection: theoretical results," *Proceedings of the 9th IEEE Computer Security Foundations Workshop*, Kenmare, Ireland, pp. 18-26, 1996.
- [68] Patrik D'haeseleer, S. Forrest, and P. Helman, "An immunological approach to change detection: algorithms, analysis and implications," *IEEE Symposium on Security and Privacy*, Oakland, CA, USA, pp. 110-119, 1996.
- [69] Paul E. M. Fine, Herd Immunity: History, Theory, Practice *Oxford Journals, Epidemiologic Reviews*, vol. 15, pp. 265-302, 1993.
- [70] Paul S. Andrews and Jon Timmis, "Inspiration for the Next Generation of Artificial Immune Systems," *Proceedings Artificial Immune Systems: 4th International Conference, ICARIS 2005*, Banff, Alberta, Canada, pp. 126-138, 2005.
- [71] Philipp H. Mohr, Nick Ryan, and Jon Timmis, "Exploiting Immunological Properties for Ubiquitous Computing Systems," *Proceedings Artificial Immune Systems: Third International Conference, ICARIS 2004*, Catania, Sicily, Italy, pp. 277-289, 2004.
- [72] R. M. Anderson and R. M. May, Vaccination and herd immunity to infectious diseases *Nature*, vol. 318, pp. 323-329, Nov 28, 1985.
- [73] Ray Paton. Introduction to computing with biological metaphors. In: *Computing With Biological Metaphors*, ed. Ray Paton. London, UK: Chapman & Hall, 1994.pp. 1-8.
- [74] Roy M. Anderson, Modern vaccines: immunisation and herd immunity *The Lancet*, vol. 335, pp. 641-646, Mar 17, 1990.
- [75] Scott Aaronson, NP-complete problems and physical reality *ACM SIGACT News (COLUMN: Complexity theory)*, vol. 36, no. 1, pp. 30-52, 2005. ACM Press. New York, NY, USA.
- [76] Simon M. Garrett, How do we evaluate artificial immune systems? *Evolutionary Computation*, vol. 13, pp. 145-177, 2005.
- [77] Stephanie Forrest, Alan S. Perelson, Lawrence Allen, and Rajesh Cherukuri, "Self-Nonself Discrimination in a Computer," *Proceedings of the 1992 IEEE Symposium on Security and Privacy*, pp. 202-212, 1994.
- [78] Stephanie Forrest and S. A. Hofmeyr. Immunology as Information Processing. In: *Design Principles for the Immune System and Other Distributed Autonomous Systems*, ed. Lee A. Segel, I. R. C. New York: Oxford University Press, 2001.pp. 361-388.
- [79] Stephanie Forrest, S. A. Hofmeyr, A. Somayaji, and T. A. Longstaff , "A Sense of Self for Unix Processes ," *Proceedings of the 1996 IEEE Symposium on Security and Privacy*, Oakland, CA, USA, pp. 120-128 , 1996.
- [80] Stephanie Forrest, Steven A. Hofmeyr, and Anil Somayaji, Computer immunology *Communications of the ACM*, vol. 40, pp. 88-96, Oct, 1997.
- [81] Steven A. Hofmeyr, Stephanie Forrest, and Anil Somayaji, Intrusion Detection using Sequences of System Calls *Journal of Computer Security*, vol. 6, pp. 151-180, 1998.
- [82] Steven Hofmeyr and Stephanie Forrest, "Immunity by Design: An Artificial Immune System," *Proceedings of the Genetic and Evolutionary Computation Conference (GECCO)*, San Francisco, CA, USA, pp. 1289-1296, 1999.
- [83] Steven Hofmeyr, Stephanie Forrest, and Patrik D'haeseleer, "An Immunological Approach to Distributed Network Intrusion Detection," *First International Workshop on the Recent Advances in Intrusion Detection (RAID'98 Symposium)*, Louvain-la-Neuve, Belgium, 1998.
- [84] Stuart J. Russell and Peter Norvig. *Artificial Intelligence: A Modern Approach*, Prentice Hall, 1995.
- [85] Susan Stepney, Robert E. Smith, Jonathan Timmis, and Andy M. Tyrrell, "Towards a Conceptual Framework for Artificial Immune Systems," *Proceedings Artificial Immune Systems: Third International Conference, ICARIS 2004*, Catania, Sicily, Italy, pp. 53-64, 2004.
- [86] Susan Stepney, Robert E. Smith, Jonathan Timmis, Andy M. Tyrrell, Mark J. Neal, and Andrew N. W. Hone, Conceptual Frameworks for Artificial Immune Systems *International Journal of Unconventional Computing*, vol. 1, pp. 315-338, Jul, 2005.
- [87] Thomas Knight and Jon Timmis, "AINE: An Immunological Approach to Data Mining," *First IEEE International Conference on Data Mining (ICDM'01)*, San Jose, CA, USA, pp. 297-304, 2001.
- [88] W. P. Glezen and M. Alpers, Maternal immunization *Clinical infectious diseases, International Conference on Acute Respiratory Infections*, vol. 28, pp. 188-239, 1999.
- [89] Witold Pedrycz. *Computational Intelligence: An Introduction*, New York: CRC Press, 1997.
- [90] Yoshiteru Ishida, "Fully distributed diagnosis by PDP learning algorithm: towards immune network PDP model," *IJCNN International Joint Conference on Neural Networks*, San Diego, CA, USA, pp. 777-782, 1990.
- [91] Yoshiteru Ishida, "The immune system as a prototype of autonomous decentralized systems: An overview," *3rd International Symposium on Autonomous Decentralized Systems (ISADS '97)*, Berlin, Germany , pp. 85-92, 1997.