Cognition, Immunology, and the Cognitive Paradigm

JASON BROWNLEE
Technical Report 070504A
Complex Intelligent Systems Laboratory, Centre for Information Technology Research,
Faculty of Information and Communication Technologies, Swinburne University of Technology
Melbourne, Australia
jbrownlee@ict.swin.edu.au

***Abstract*-Cognition is the study of higher-level information-processing mechanisms not limited to the perception, transformation, application, and storage of knowledge. A relatively new paradigm of immunology takes a systems and cognitive perspective, proposed as a replacement for the dogmatic clonal selection theory and the deficiencies of the self-nonself discrimination pattern. This work reviews the cognitive paradigm of immunity with an eye for exploiting such work in the design of computational intelligence algorithms.**

Keywords- Cognition, Immunology, Cognitive Paradigm, Clonal Selection Theory, Artificial Immune Systems

I. Introduction

The conventional clonal selection theory of immunity promotes a view of the acquired immune system as the discrimination between self and nonself. An alternative perspective of immunity is to consider a holistic system in which collectives of varied cells and molecules communicate and coordinate a response in the context of antigen perception. This view is called the cognitive paradigm of immunity proposed by Irun Cohen. This work provides a brief review of Cohen's paradigm and some related works.

Section II introduces the cognitive paradigm of information processing as proposed by de Mey, an interpretation that underlies Cohen's perspective of immunity. Section III summarise the cognitive paradigm of immunity, highlighting some deficiencies of the clonal selection theory, the proposed immunological homunculus and the tradition of cognitive lexicon in immunological theory. Section IV reviews some related work, specifically emergent specificity, a language metaphor that extends the cognitive paradigm, and how the paradigm may be used to consider the computational properties of the biological system.

II. Cognitive Paradigm

Cognitive science is the study of knowledge, which includes questions regarding what knowledge is and how knowledge may be manipulated and transformed [28]. The study of cognition is strongly multi-disciplinary with has roots in neuroscience, computer science, philosophy, and psychology (among other fields). Cognition is a broad term and has varied means across the different fields of study, all loosely related to information processing. In investigating cognition one may be interested in *learning* and the memory and adaptation properties of knowledge manipulation, in *reasoning* and the application of knowledge in decision making and planning, in *beliefs* and abstractions and generalizations of knowledge, or in *intelligence* and the theory of mind.

Cognition may be seen as the pinnacle in a classification series of four information-processing stages ([28]), as follows:

Monadic (*pattern recognition*): Information units are handled independently of each other. Examples include simple pattern recognition using isolated and monolithic units.
Structural (*feature analysis*): Several information units arranged in some way. Example is an extension of a monadic system that uses structural features of the pattern in a feature analysis
Contextual (*contextual analysis*): The structural organization of information units as well as the use of higher-level domain knowledge and information processing. Example includes making use of the context of the pattern matching and feature analysis.
Cognitive (*analysis by synthesis*): Information supplements a conceptual information processing system that has a model of the world. Discrimination of features and context based on an internal model of the world.

Figure 1 – A four-stage classification of information processing, (from [28])

An example of the above stages of information processing that culminate in a cognitive system is language processing. Mey discusses how the four stages apply to this example, and the previous example of pattern matching both of which may be implemented in an Artificial Intelligence (AI).

Knowledge and information	AI pattern recognition and perception	AI language processing and communication
Monadic	Template matching	Word-to-word translation
Structural	Feature analysis	Syntactical analysis
Contextual	Context analysis	Indexical expressions
Cognitive	Analysis by synthesis	World models

Table 1 - Phrasing of pattern matching and language processing in the four stages of information processing (from [28], pg. 16)

A cognitive perspective in AI is a shift from the object and the signal, to the subject or the receiver (cognitive system). The problem of cognition is how to get a representation into the cognitive system. One may favour a passive system that is highly receptive to its environment, where any cognitive activity is seen as oriented toward a maximum exposure to 'stimulation'. Stimulation in isolation has no meaning, instead a strong organizational relationship between subject and object mean the stimuli evoke or confirm aspects of the systems internal model. The second major shift is from units in isolation to a hierarchal complex of models and messages. Large models are required to store the experience and worldview to understand the simplest of messages. The model needs to anticipate what it will perceive, but it must perceive more than it anticipates, otherwise there is no reason to perceive.

III. Cognitive Paradigm of Immunity

The cognitive paradigm of immunology refers to the work by Cohen (and collaborators) which evolved from perceived deficiencies of the clonal selection theory, his immunological homunculus theory, and from his considering of the immune system in light of Mey's cognitive paradigm. Although not the first to either use cognitive nomenclature in immunology, or consider the immune system as performing cognition, the theory provides a strong case for a replacement for clonal selection as a model of immunity [22].

A. *Clonal Selection Theory and Problems*

The clonal selection theory of Burnet [9-11] and Talmage [3,4] both inspired by Jerne's antibody selective theory [29] explains the diversity of antibodies and their tolerance to self tissues. The essence of the theory, is that those lymphocyte cells with receptors that can bind to antigen proliferate and flourish, and that antigen receptors for self-tissues are forbidden (such cells are destroyed). The theory describes a process for refining the specificity of a potentially very large repertoire of lymphocytes (specifically their receptors) to something that is useful and meaningful to the host in its antigenic environment. The antigen-antibody (pattern recognition) centric theory has led a generation of immunologists to consider that the function of the immune system is to discriminate between self and nonself.

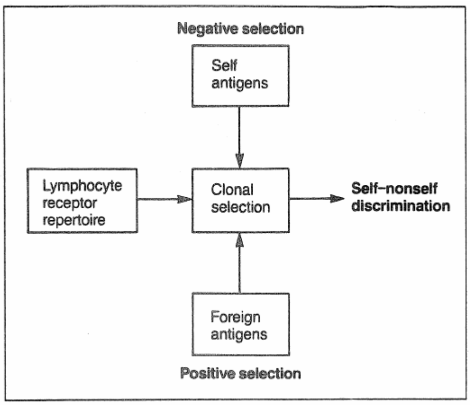

Figure 2 - Summary of clonal selection theory (taken from [16] page 491)

Many have criticized specific aspects of this theory, and alternative theories and extensions have been proposed. These alternatives are not limited to an idiotypic network theory by Jerne [30-33], and Matzingers danger theory [35-37].

A founding principle of Cohen's cognitive paradigm, and immunological homunculus, is in the need to address observations of which the clonal selection theory (CST) cannot account. In [17], Cohen lists a numerous immunological observations unaccounted by CST, which include: antigen processing antigen presentation, the structure and function histocompatibility complex (MHC) molecules, multicellular interactions, restrictions in T-cell receptor and antibody gene usage, superantigens, cytokine functions and networks, suppression and anti-idiotypes. Further, he proposes that a corollary of clonal selection regarding autoimmunity is contradicted (discussed next). It is important to point out that the attack on CST by Cohen is the original theory proposed by Burnet, and that there is argument that the specifics of his theory may be divorced from the theories core principles which describes how antibodies are formed, not why they are formed [2].

B. *The Immunological Homunculus*

The clonal selection theory suggests that autoimmunity is the result of leaks in the maturation process where antigen receptors for self evade the negative selection process. In [17,24], Cohen comments (1) that autoimmunity is not a defect, rather a property of all healthy immune systems, and (2) some autoimmunity is highly structured and predictable, even uniform. These observations regarding autoimmunity were used as the basis of Cohen's immunological homunculus (immunculus), which suggests that self-reacting receptors are kept in check by regulatory networks, and that such receptors respond in an altered context [14,15,18,19,24].

The *homunculus* refers to a theory that an internal image of self (homunculus means 'little man') is encoded in groups of neurons of the central nervous system based on observations from cognitive neuroscience such as phantom limbs. Using the same analogy, the *immunological homunculus* suggests that the immune system encodes a mirror image of the molecular self in self-reacting lymphocytes providing a theory to support natural autoimmunity. This image of molecular self is skewed in that it is comprised of a set of dominant self-antigens. Cohen proposes that autoimmunity is selected for by evolution, that it is kept in check by regulatory networks, and that it comes into effect to fight tumours, and microbial antigens that have self-like receptors (antigenic mimicry) [21].

C. *Cognitive Tradition*

Use of a cognitive lexicon has a long tradition in the theories of immunology, particularly with regard to the systems perception, acquisition, and processing of information [13]. Fundamentally, the ideas of antigen-antibody interaction are described as pattern recognition. The CST is concerned with learning or training via affinity maturation, and the acquired immunity is maintained through the use of memory mechanisms (memory B and T lymphocyte cells).

Jerne's network theory [30] is fundamentally cognitive [13], in that it proposes a network of interacting receptors where holistically, the system knows itself. A cognitive interpretation of the immune system called '*self-assertion*' was proposed by Varela and Coutinho (and colleagues) [1,5-8,26] that is an extension of network theory and involves dynamic patterns of recognition without explicit self and nonself. Finally, Grossman and Paul also describes the immune system as being cognitive [42-44], where discrimination is about the intensity of stimulation and suppression signals in context.

D. *A Holistic Perspective*

Leveraging the immunological homunculus as an internal model of the molecular environment, Cohen proposed his cognitive theory of immunology as a replacement for the (incomplete and obsolete) clonal selection theory [16,17]. The interaction of antigen and receptors and the resultant clonal expansion and maturation are taken as fact, thus Cohen maintains CST as an explanation for clonal activation. Unlike CST, the theory proposes a holistic perspective of the immune system that proposes that the system is cognitive and a complement to the central nervous system to which it is tightly integrated.

Cohen proposes that the task of the immune system may be to protect the host from death by infection, and with this in mind he proposes three problems faced by the immune systems (Figure 3).

The signal/noise problem (*how to focus recognition*): The receptors of B and T lymphocytes can recognise a vast array of amino acids and protein conformations. A single molecule may have many different antigenic determinants. The immune system must filter out those non-critical (to survival) determinants and focus on those that are hazardous.
The context problem (*when to act*): Context provides information as to whether or not the antigenic determinant is a hazard or is harmless. It provides additional information to the filtering process as to when to attack, and when not to do so.
The response problem (*how to choose the most suitable immune effect*): Recognition is not a Boolean operation; it is a function of the quantity, quality, timing, and location of the event. The response provided (what the system can do) is based upon the repertoire of receptors (what the system can see) .

Figure 3 - Summary of problems faced by immune system (taken from [17])

As a paradigm, antigen-receptor interaction is about interpretation of antigen (whatever its origin) in the context of where it is perceived, and based upon this perception, the system selects an appropriate response. The aggregation of this behaviour results in an emergent intentionality of the system. The CST was about a passive clone reacting to the arrival of an antigen. The cognitive paradigm encompasses the problems faced by the immune system where collectively the processes of the system filter and perceive antigens in context and respond accordingly. The internal image (worldview provided by the immunological homunculus) guides and restricts clonal activation.

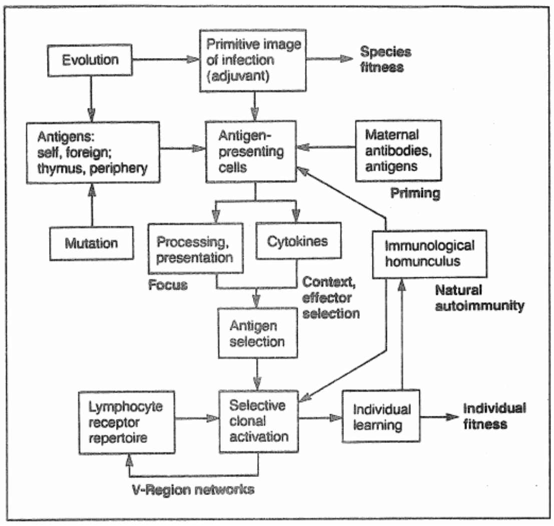

Figure 4 - The cognitive paradigm of immunity (taken from [16] page 493)

This holistic perspective defines a system (rather than an interaction) that is dynamic, hierarchal, and self-organizing [22]. The system accounts for the lack of one-to-one correspondence with antigen and receptor (degeneracy) as proposed by CST. It proposes how the immune system is capable of generating specificity for antigen out of the non-specificity of its parts (co-respondence) without intrinsic notions of foreignness and non-foreignness.

In [17], Cohen proposes the cognitive principle is the definition and creation of information by internal representations and the intentionality of the system. In [22], Cohen proposes that a cognitive system (1) contains internal images of its environment, (2) is self organizing in updating its internal images, and (3) makes decisions based upon its internal state. One may link the paradigm back to Mey's four stages of information processing, as follows.

Knowledge and information	**Cognitive Paradigm of Immunity**
Monadic	Pattern matching such antigen-antibody (clonal activation)
Structural	Filtering such and focusing such as antigen presenting cells
Contextual	Location and timing of exposure, inflammation, etcetera
Cognitive	Integrated system, the cognitive paradigm

Table 2 - Phrasing of the cognitive paradigm against Mey's four stages of information processing

In [25], Cohen, et al. directly compares and discusses CST and the cognitive theory using seven features of the immune system, which they summarize to a table (Table 3). The cognitive theory may be reduced to ideas of inflammation and specificity as emergent effects from the interaction and dialog between varied components (B-cells, T-cells, molecules, etcetera), and the co-response (corespondence) or decision making by committee [20].

No.	Feature	Specificity paradigms	
		CST paradigm	Cognitive paradigm
1	Specificity	Intrinsic property	Emergent property
2	Functional unit	Individual clone	Cell collective; anatomy
3	Action	Clonal response	Co-response; modeling
4	Discourse	Monolog	Dialog–symposium
5	Output	Discrimination	Inflammation
6	Objective	Defense	Maintenance
7	Genetics	Meta-germline	Germline & meta-germline

Table 3 – Comparison of the clonal selection and cognitive theories

IV. Some Related Work

This section discusses some interesting work by Cohen and collaborates related to and extending the cognitive paradigm of immunity. This section elaborates on emergent specificity, the dialog between cells, and ideas of immune computation.

A. *Degeneracy and Emergent Specificity*

There is a lack of a one-to-one correspondence between antigen and receptor. A given antigen may have the capacity to trigger a very larger number of receptors, thus resulting in a *polyclonal activation*, although a response is typically oligoclonal. This may be accounted for by the competition between clones for selection by the antigen. In addition, a given receptor may respond to a large number of antigens, thus resulting in a *polyclonal response*, something that cannot be accounted for by the clonal selection theory. Cohen refer to this polyclonal response of a given receptor as cellular degeneracy, where, without context, receptors are cross-specific that includes auto-specificity [25].

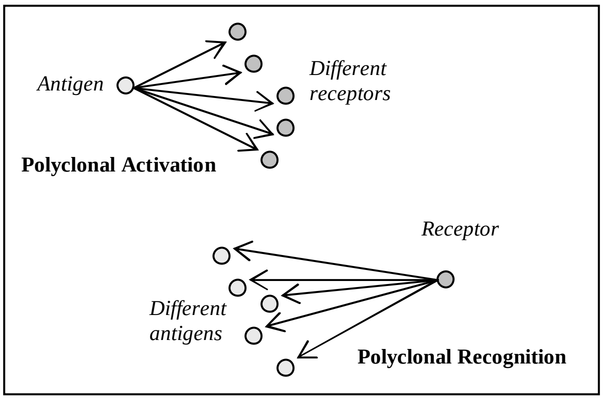

Figure 5 - Depiction of a polyclonal activation and a polyclonal response

Given that a typical immune response is highly specific, how does the immune system account for the discrimination between receptors? A polyclonal response is the antithesis of clonal dominance, a feature that underlies the clonal selection theory. The solution as proposed in cognitive theory is that specificity is an emergent phenomenon [21,40]. Unlike CST, where specificity is a property of antigen-receptor interaction, emergent specificity is a down-stream effect that occurs after the initial interaction. A collection of varied and communicating cell types respond to the antigen in context. This is the so-called meta-response of cognitive theory, called the co-response or corespondence. The degeneracy of cell signalling is proposes as the basis of plasticity both in the brain and in the immune system, and is the feature exploited by antibiotics and pharmaceuticals [20].

B. *Language Metaphor of Immunity*

Atlan and Cohen elaborate on the cognitive theory, in particular the need for context and the communication between cellular components, proposing a language metaphor of immunity [12,20]. The immune chemical-based language (like human language) has syntax and abstractions. The syntax is the context that connects ontogenetically different cells and molecules together to form actions. The abstractions are provided by the systems processes that break antigen into fragments for presentation such that these fragments are used as generalizations of the antigen epitope. Using this metaphor, the antigen is taken as the noun (subject or address) of the immune sentence, and the germ-line signals and information acquired through experience are the predicates on the noun, which select a response. Thus, unlike the CST, and danger theories, which propose that the immune system operates towards a goal (teleological), the cognitive theory proposes that the immune system defines its own meaning as an emergent property through its interaction with antigen.

Atlan and Cohen [12] also invoke a theory of system complexity from noise. The theory proposes (1) hierarchal multilevel organization, where information is lost through mutations to gene's during a clonal activation, although this local loss promotes a global gain in information. To support this feature, the system requires (2) the redundancy of information through duplication (clones) and a polyclonal response, such that when a mutation occurs during the coping process, the loss is not the only copy.

Linguistics and information theory do provide an interesting perspective on the immune system, and the cognitive theory in particular, although such exercises in metaphor require a mechanistic grounding [38].

C. *Immune Computation*

Computation and artificial intelligence are heavily influenced by cognitive properties [34,39]. In [23], Cohen proposes that the immune system, and the cognitive theory of immunity in particular provide a interesting basis for such pursuits.

"*A cognitive theory of the immune system, in contrast to the clonal selection theory, is computational in spirit and practice*".

The immune system takes the state of the body as input and outputs a healing process (inflammation) to maintain the body. Cohen compares the immune system with a computer firstly contrasting the two, and secondly highlighting some of the advantages of the biological system with regard to computation (summarised in Table 4).

Things immune systems are not	Things computers cannot do
No external operator or programmer	Self assembly
No algorithms or software (hardware and software are one and the same)	Continuous replication (proliferation of cells)

No central processing unit (CPU)	Continuous death (death and removal of cells)
No standard operating system (all different)	Distributed in space (cells roam)
No formal mathematic logic (messy)	Ad hoc organization (cells get together and interact when required)
No termination criterion	Memory is based on experience (evolution and somatic)
No verification processes	Dismantled system still works (cells in culture)

Table 4 - Summary of the differences between the immune system and a computer, and advantages of immune computation

Cohen goes on to define immune computation as a series of computational properties that embody some of the interesting aspects of the information processing performed by the immune system.

Always on: The immune system has no termination criterion, it is a continually reacting computer system, forever assessing and updating its state, and ceases functioning when the host dies.
Data are the program: No distinction between hardware and software, with no programmer or central processing unit.
Parallel processing: Each cell in the system may be considered a processor. Computation emerges from all the processors in the system working and networking together in an ad hoc manner to provide a dynamic response (in space and time).
Anatomy facilitated networking: The cells migrate around the body using regular flows in of the blood and lymph with variable residence in lymphoid tissues. Haphazard congestion results in interactions, where low level properties that govern individual cell positions are stochastic, the high-level dynamics of the system are highly organized.
Cellular diversity: Individual processes are distinct, with different information processing properties. Cells interact with each other in neighbourhoods using communication.
Integration (co-respondence): cells patrol and act on the perceived local state which includes the state of the system and the actions of other cells. The dynamic situation response called co-respondence provides the high-level information processing units of the system. Collectives of cells provide the decision-making mechanism.
Adaptation: Individual components die, are generated randomly, and are adapted dynamically. Changes to the genes of individual cell receptors collectively personalise the system based on the hosts antigenic environment.

Figure 6 - Summary of the complexities of the immune system from a computation perspective

Also discussed are the scales of computation (cell, clones, system, host, species, society, etc.), and the immunological homunculus (already discussed). Cohen rounds of his treatment of immune computation focusing on the challenges of immunology and the contribution computer science may make in modelling the complexities of the system.

V. DISCUSSION

The cognitive theory of immunity provides a natural interpretation of the mechanisms of the acquired immune system for the design of computational intelligence systems. In particular, the de-centralized properties of recognition and response embodied in emergent specificity suggest a natural mode of autonomous systems design, a point that has not gone unnoticed [27,41].

How might one replicate the co-respondence effect for other purposes? Can such an effect be achieved through diversity and inter-communication of a single class of functional unit, or is a multi-step cast system required like the recognition, presentation, and effector casts of the acquired immune system? Autonomy plays an important role in the organization of the discrete units, facilitating context via guiding the space and time qualities of antigen exposure to heterogeneous (in function and specificity) cells and molecules. Much work remains, not limited to an effective literature review of how this theory has already been used as a basis for biologically inspired computation.

ACKNOWLEDGMENTS

Tim Hendtlass for his patience and for providing useful feedback on drafts of this paper

REFERENCES

[1] A. Coutinho, L. Forni, D. Holmberg, F. Ivars, and N. Vaz, From an Antigen-Centered, Clonal Perspective of Immune Responses to an Organism-Centered, Network Perspective of Autonomous Activity in a Self-Referential Immune System *Immunological Reviews*, vol. 79 , pp. 151–168Jun, 1984.

[2] Arthur M. Silverstein, The Clonal Selection Theory: what it really is and why modern challenges are misplaced *Nature Immunology*, vol. 3, pp. 793-796, 2002.

[3] D. W. Talmage, Allergy and Immunology *Annual Review of Medicine*, vol. 8, pp. 239-256, 1957.

[4] David W. Talmage, Immunological specificity: Unique combinations of selected natural globulins provide an alternative to the classical concept *Science* , vol. 129, pp. 1643-1648, 1959.

[5] F. J. Varela, A cognitive view of the immune system *World Futures*, vol. 42, pp. 31-40, 1994.

[6] F. J. Varela and A. Coutinho. Immunknowledge: the immune system as a learning process of somatic individuation. In: *The Reality Club*, ed. J. E. Brockman. New York: Prentice Hall Press, 1991.pp. 237-256.

[7] F. J. Varela and A. Coutinho, Second generation immune networks *Immunology Today*, vol. 12, pp. 159-166, 1991.

[8] F. Varela, A. Coutinho, B. Dupire, and N. N. Vaz, Cognitive networks: immune, neural and otherwise *Theoretical Immunology: Part II (SFI Studies in the Sciences of Complexity)*, vol. 2, pp. 359-371, 1988.

[9] 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.

[10] Frank Macfarlane Burnet. *The clonal selection theory of acquired immunity*, Nashville, Tennessee, U.S.A.: Vanderbilt University Press, 1959.

[11] Frank Macfarlane Burnet, Clonal selection and after *Theoretical Immunology*, vol. pp. 63-85, 1978.

[12] H. Atlan and Irun R. Cohen, Immune information, self-organization and meaning *International Immunology*, vol. 10, pp. 711-717, 1998.

[13] I. A. Tauber, Historical and Philosophical Perspectives Concerning Immune Cognition *Journal of the History of Biology*, vol. 30, pp. 419-440, 1997.

[14] Irun R. Cohen. Natural Id-Anti-Id Networks and the Immunological Homunculus. In: *Theories of Immune Networks*, eds. H. Atlan and Irun R. Cohen. Berlin: Springer-Verlag, 1989.pp. 6-12.

[15] Irun R. Cohen. The immunological homunculus and autoimmune disease. In: *Molecular Autoimmunity*, ed. N. Talal. USA : Academic Press, 1991.pp. 438-453.

[16] Irun R. Cohen, The cognitive paradigm and the immunological homunculus *Immunology Today*, vol. 13, pp. 490-494, 1992.

[17] Irun R. Cohen, The cognitive principle challenges clonal selection *Immunology Today*, vol. 13, pp. 441-444, 1992.

[18] Irun R. Cohen. Kadishman's Tree, Escher's Angels, and the Immunological Homunculus. In: *Autoimmunity: Physiology and Disease*, eds. Antonio Coutinho and Michael D. Kazatchkine. Wiley-Liss, Inc, 1994.pp. 7-18.

[19] Irun R. Cohen, Treatment of autoimmune disease: to activate or to deactivate? *Chemical Immunology*, vol. 60, pp. 150-60, 1995.

[20] Irun R. Cohen, Discrimination and dialogue in the immune system *Seminars in Immunology*, vol. 12, pp. 215-219, 2000.

[21] Irun R. Cohen, Antigenic Mimicry, clonal selection and autoimmunity *Journal of Autoimmunity*, vol. 16, pp. 337-340, 2001.

[22] Irun R. Cohen. *Tending Adam's Garden: Evolving the Cognitive Immune Self*, New York: Academic Press, 2001.

[23] Irun R. Cohen, "Immune System Computation and the Immunological Homunculus," *Proceedings Model Driven Engineering Languages and Systems, 9th International Conference, (MoDELS 2006),* Genova, Italy, pp. 499-512, 2006.

[24] Irun R. Cohen and D. B. Young, Autoimmunity, microbial immunity and the immunological homunculus *Immunology Today*, vol. 12, pp. 105-110, 1991.

[25] Irun R. Cohen, U. Hershberg, and S. Solomon, Antigen-receptor degeneracy and immunological paradigms *Molecular Immunology*, vol. 40, pp. 993-996, 2004.

[26] J. Stewart, Cognition without neurones : adaptation, learning and memory in the immune system *CC-AI*, vol. 11, pp. 7-30, 1993.

[27] 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.

[28] Marc de Mey. *The Cognitive Paradigm: An Integrated Understanding of Scientific Development (Sociology of the sciences monographs)*, USA: D. Reidel Publishing Company, Kluwer Academic Publishers Group, 1992.

[29] 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.

[30] N. K. Jerne , Towards a network theory of the immune system *Annals of Immunology*, vol. 125, pp. 373-389, Jan, 1974.

[31] N. K. Jerne, The immune system: a web of V-domains *Harvey lectures*, vol. 70, pp. 93-110, 1976.

[32] N. K. Jerne , Idiotypic networks and other preconceived ideas *Immunological Reviews*, vol. 79, pp. 5-24, 1984.

[33] Niels K. Jerne, The generative grammar of the immune system *Bioscience Reports*, vol. 5, pp. 439-451, 1985.

[34] P. J. Hayes , Computer programming as a cognitive paradigm *Nature*, vol. 254, pp. 563-566, 1975.

[35] Polly Matzinger, Tolerance, danger, and the extended family *Annual Review of Immunology*, vol. 12, pp. 991-1045, 1994.

[36] Polly Matzinger, An innate sense of danger *Seminars in Immunology* , vol. 10, pp. 399-415, Oct, 1998.

[37] Polly Matzinger, The Danger Model: A Renewed Sense of Self *Science*, vol. 296 , pp. 301-305, 2002.

[38] Rodney E. Langman and Melvin Cohn , Away with words: commentary on the Atlan-Cohen essay 'Immune information, self-organization and meaning' *International Immunology*, vol. 11, pp. 865-870, Jun, 1999.

[39] Stuart J. Russell and Peter Norvig. *Artificial Intelligence: A Modern Approach*, Prentice Hall, 1995.

[40] U. Hershberg, S. Solomon, and Irun R. Cohen, "What is the basis of the immune system's specificity?," *Mathematical Modelling & Computing in Biology and Medicine,* pp. 377-384, 2003.

[41] 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.

[42] Z. Grossman and W. E. Paul , Adaptive Cellular Interactions in the Immune System: The Tunable Activation Threshold and the Significance of Subthreshold Responses *Proceedings of the National Academy of Sciences* , vol. 89, pp. 10365-10369, 1992.

[43] Zvi Grossman, Cellular Tolerance as a Dynamic State of the Adaptable Lymphocyte *Immunological Reviews*, vol. 133, pp. 45–73Jun, 1993.

[44] Zvi Grossman and William E. Paul, Autoreactivity, dynamic tuning and selectivity *Current Opinion in Immunology*, vol. 13, pp. 687-698, Dec, 2001.