An Immune Algorithm based on the Complement Activation Pathway

Chen Guangzhu†,††, Li Zhishu†, Yuan Daohua†, Nimazhaxi† and Zhai yusheng ††

†School of Computer, Sichuan University, Chengdu, 610065 P.R.China
††College of Mechanical & Electrical Engineering, China University of Mining and Technology, Xuzhou, 221008 P.R.China

Summary
Artificial Immune System (AIS) is a novel evolutionary paradigm inspired by the biological immune system. The models based on immune system principles, such as the clonal selection theory, the immune network model or the negative selection algorithm, have been finding increasing applications in fields of science and engineering. The presented algorithms only simulates a little of principles of the immune system. Since the immune system is a complex biologic system, which includes many principles, which can offer elicitations for engineering application. The complement system, which represents a chief component of innate immunity, not only participates in inflammation but also acts to enhance the adaptive immune response. In the complement system, the activation of complement proteins are really the evolution processes of complement proteins, in which, complement proteins cleave and bind, finally forms a complex resulting in an impairment of osmotic regulation and subsequent cytolysis .In this paper, we develop a novel immunological algorithm based on the complement system-An Immune Complement Algorithm (ICA). ICA mainly simulates the classical pathway of the complement system. In the algorithm, two operators: cleave operator and bind operator are presented, cleave operator cleaves a complement individual into two sub-individuals, while bind operator binds two individuals together and forms a big individual. The experiments of ICA compared with the standard genetic algorithm (SGA) and the clonal selection algorithm (CSA) are implemented. The experiment results show that ICA is better than SGA and CSA. ICA offers new elicitations for engineering application.

Key words:
Artificial immune system, Complement system, Immune complement algorithm, Cleave operator, Bind operator

1. Introduction

Biological studies have always constituted a large pool of inspiration for the design of engineering systems. These last decades, two biological systems have provided a remarkable source of inspiration for the development of new types of algorithms: they are neural networks and evolutionary algorithms.

In recent years, another biological inspired system has attracted the attention of researchers, the natural immune system and its powerful information processing capabilities. In particular, it performs many complex computations in a highly parallel and distributed fashion. The key features of the immune system, which provide several important aspects to the field of information processing, are: recognition, feature extraction, diversity, learning, memory, self-regulation, distributed detection, probabilistic detection, adaptability, specificity, etc.

It is to be noted that the mechanisms of the immune system are remarkably complex and poorly understood, even by immunologists. Several theories and mathematical models have been proposed to explain the immunological phenomena. There are also a growing number of computer models called Artificial Immune System (AIS) to simulate various components of the immune system and the overall behavior from the biological point of view [1]. The models based on immune system principles, such as the clonal selection theory [2], the immune network model [3,4,5] or the negative selection algorithm [6], have been finding increasing applications in fields of science and engineering [7] such as: computer security, virus detection, process monitoring, fault diagnosis, pattern recognition, etc.

Although the number of specific applications confirms the interest and the capabilities of these principles, the lack of a general purpose algorithm for solving problems based on them contrasts with the major achievements in that are for other biologically inspired models, and the presented algorithms only simulates a little of principles of the immune system. Since the immune system is a complex biologic system, which includes many principles, which can offer elicitations for engineering application.

The complement system, which represents a chief component of innate immunity, not only participates in inflammation but also acts to enhance the adaptive immune response. Specific activation of complement via innate recognition proteins or secreted antibody releases cleavage products that interact with a wide range of cell surface receptors found on myeloid, lymphoid and stromal cells. This intricate interaction among complement

Manuscript revised August 22, 2005.

activation products and cell surface receptors provides a basis for the regulation of both B and T cell responses [8].

The activation pathways of the complement system are really evolution processes of complement proteins, in which, complement proteins cleave and bind, finally form a complex resulting in an impairment of osmotic regulation and subsequent cytolysis .In this paper, we develop a novel immunological algorithm based on the complement system-An Immune Complement Algorithm (ICA). ICA mainly simulates the classical pathway of the complement system. In this algorithm, two operators: cleave operator and bind operator are presented, cleave operator cleaves a complement individual into two sub-individuals, while bind operator binds two individuals together and forms a big individual. Compared with other algorithms, there are a few of manual parameters in ICA. The experiments of ICA compared with the standard genetic algorithm (SGA) and the clonal selection algorithm (CSA) are implemented. The results show that ICA is better than SGA and CSA.

The paper is organized as follows. Section II and section III introduce the complement system and the classic pathway respectively. In the section IV, an immune complement algorithm is presented. Section V describes experiments and analysis. Section VI concludes the discussion of the set-up and future work.

2. The Complement system

Sometimes the interaction of antibodies with antigen is useful by itself in the immune system, For example, coating a virus or bacterium thus preventing it from binding to — and invading — a host cell (e.g., antipolio antibodies); Binding to a toxin molecule (e.g., diphtheria or tetanus toxin) thus keeping the toxin from entering a cell where it does its dirty work. But most of the time, the binding of antibodies to antigen performs no useful function until and unless it can activate an effector mechanism.

The complement system is a kind of the effector mechanism. The complement system refers to a series of proteins circulating in the blood and bathing the fluids surrounding tissues. The proteins circulate in an inactive form, but in response to the recognition of molecular components of microorganism, they become sequentially active, working in a cascade where in the binding of one protein promotes the binding of the next protein in the cascade. The complement system consists of some 30 proteins circulating in blood plasma. Most of these are inactive until they are cleaved by a protease, which, in turn, converts them into a protease. Thus many components of the system serve as the substrate of a prior component and then as an enzyme to activate a subsequent component. This pattern of sequential activation produces an expanding cascade of activity.

The biological effects of the complement system are:

(i) Opsonisation. The C3b and, to a lesser degree, C4b molecules are opsonins. That is they coat foreign organisms either by the AP or those already bound by antibody. Opsonisation of particles greatly enhances their phagocytosis by means of binding to specific complement receptors.

(ii) Inflammation. The C5a and, less potently, the C4a and C3a fragments are important inflammatory activators inducing vascular permeability, recruitment and activation of phagocytes.

(iii)Lysis. C5b binds and recruits C6 and C7 to the target surface. C7 and subsequently C8 change conformation to expose hydrophobic domains, which insert in the lipid bilayer. The C5b678 complex catalyses the polymerisation of the final component C9 which forms a transmembrane pore of ~ 10nm diameter causing lysis of the cell. This macromolecular assembly is known as the Membrane Attack Complex (MAC).

(iv)Immune complex clearance. Complement has a very important role in solubilising and causing removal from the circulation of immune complexes. It does this by the binding of C4b and C3b, covalently bound to the immune complex, to CR1 complement receptors on red blood cells which transport the complexes to the liver and spleen where they give the complexes up to phagocytes for destruction.

All the above biological effects are realized through the complement activation pathways. There exist three complement activation pathways: the classical pathway, the lectin pathway, and the alternative pathway:

(i) The classical complement pathway is activated by antigen-antibody complexes.

(ii) The lectin pathway is activated by the interaction of microbial carbohydrates with mannose-binding proteins in the plasma and tissue fluids.

(iii) The alternative complement pathway is activated by C3b binding to microbial surfaces and to antibody molecules.

The pathways differ in the manner in which they are activated and ultimately produce a key enzyme called C3 convertase.

3. The Classical Pathway

The classical pathway of the complement system is activated by antigen-antibody complexes that have formed on the surface of a target cell. The classical pathway is composed of three phases, which is showed in the figure 1[8]:

(i) Identify phase. Complement factor C1 binds to the Fc portion of either a single antibody molecule of IgM or to a pair of antibody molecules IgG1, IgG2, or IgG3, in apposition on the surface of the antigen. C1 is a macromolecule composed of C1q and doublets of C1r and

C1s.

C1q possesses no intrinsic catalytic activity, but when any of several activators bind to the C1q subcomponent of C1, the homologous C1r and C1s subcomponents are converted into catalytically active species, namely C1r* and C1s*, triggering the first step of the classical pathway of complement activation.

(ii)Activate phase. On binding to immune complexes through C1q, the subunits of C1 become firmly associated and auto activation commences even in the presence of the Cl-In. Initially, a conformational change in C1r occurs, followed by proteolytic activation which results in the cleavage of all four polypeptide chains of C1r2s2. The two activated C1s subunits are then able to catalyse the assembly of the C3 convertase, C4b2a, which has been formed from C2 and C4.The C1q component binds to the antibody, activating C1r and C1s to form C1 which itself has enzymatic activity to cleave C4. The cleavage of C4 releases the C4a fragment into solution and attaches the larger C4b fragment at the site, making the C14b complex, which can now bind C2. Once bound (the process is complete in 5-10 min), C2 can be cleaved by the C1 complex (or other proteolytic enzymes like trypsin or chymotrypsin). This releases the smaller C2b fragment into solution and leaves the larger C2afragment attached at the site, making the C14b2a complex. The C14b2a complex is the first of the two forms of C3 convertase.The terminal sequence of the complement system actually builds the MAC. This process is triggered when either form of C3 convertase accumulates on the target surface. C3 convertase has specific enzymatic activity to cleave C3, releasing C3a into solution and attaching the larger C3b fragment to the C3 convertase molecule at the site, making C5 convertase.

(iii) Membrane attack phase. C5 convertase has specific enzymatic activity to cleave C5, releasing both the smaller C5a fragment (a 74 amino acid glycopolypeptide) and the C5bfragment into solution. The subsequent assembly of the MAC is nonenzymatic. Fluid-phase C5b binds first C6 and then C7, forming a stable C5b67 complex. The binding of C7 converts the complex from a hydrophilic to a hydrophobic state, which then preferentially inserts the complex into lipid bilayer – including other cell membranes in the immediate vicinity of the primary surface on which complement activation is focused. C8 then binds to the C5b67 complex at a site on C5b, forming C5b678 as it inserts itself into the lipid bilayer membrane. Finally, the C5b678 complex induces C9 polymerization into the form of a hollow tubular structure, with 12-18C9 monomers attached to each C5b678 complex, completing the MAC. The MAC, a dimer of the C5b6789 complex, makes a single transmembrane channel through which water and electrolytes may pass, resulting in an impairment of osmotic regulation and subsequent cytolysis. This is similar to the action of mammalian cytolytic T lymphocytes that can kill targeted cells by inserting into their membranes a 67-kD pore-forming molecule called perforin, which has structural homology to C9. Similar molecules are found in the granules of eosinophils, various bacterial pathogens, and in the protozoan parasite Trypanosoma cruzi. Complement-mediated lysis has been shown for many kinds of cells including erythrocytes, platelets, lymphocytes, bacteria, and viruses possessing a lipoprotein envelope.

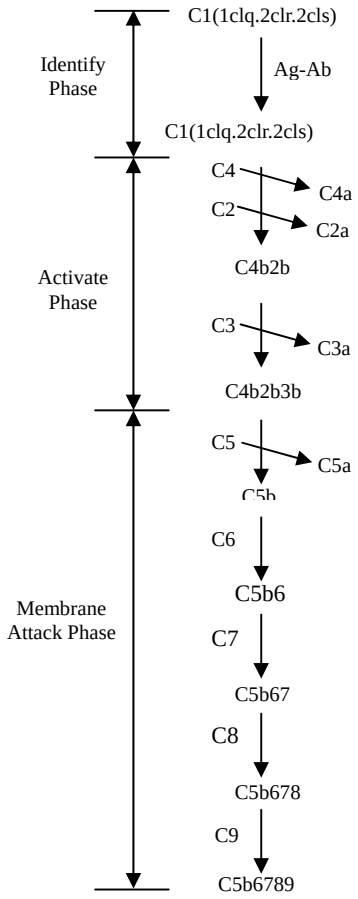

Fig.1 The classical pathway of the complement system.

4. An immune complement algorithm (ICA)

The classical pathway is evolution processes of complement molecules, in which, the complement molecules are cleaved respectively, then bind together and form a membrane attack complex, which can dissolve the plasma membrane.

In ICA, the plasma membrane, the complement and the affinities are the objective function, the feasible solution and the match degree between the solutions and the objective function, respectively.

4.1 The definition of cleave operator and bind operator

1. Cleave operator O_C

A complement individual $a=(x_1,x_2,\Lambda\ ,x_m)$, according to a cleaved probability, is cleaved in two sub-individuals: a_1 and a_2.

$$O_C(a)=\begin{cases} a_1=P_c\cdot a=(x_1,x_2,...x_{P_C}) & aff(a_1)\geq aff(a_2) \\ a_2=(1-P_c)\cdot a=(x_{(P_C+1)},x_{(P_C+2)},...,x_m) & aff(a_1)<aff(a_2) \end{cases}. \quad (1)$$

Where P_c is the cleave probability, $aff(i)$ is the affinity of the complement individual i.

2. Bind operator O_B:

Suppose there are two individuals: $a=(x_1,x_2,\Lambda\ ,x_m)$ and $b=(y_1,y_2,\Lambda\ ,y_n)$, there are two kinds of bind ways.

Positive bind operator O_{PB}:

A new individual $c=O_{PB}(a,b)$

$$=(x_1,x_2,\Lambda\ ,x_m,y_1,y_2,\Lambda\ ,y_n). \quad (2)$$

Reverse bind operator O_{RB}:

A new individual $c=O_{RB}(b,a)$

$$=(y_1,y_2,\Lambda\ ,y_n,x_1,x_2,\Lambda\ ,x_m). \quad (3)$$

4.2 The flow of ICA

ICA is composed of three phases: the identify phase, the active phase, the membrane attack phase. The flow of ICA is as follows.

Step1. Create an initial, random population of complements A_0 ($|A_0|=n$).

Step2. Termination: if the current population has contained the optimal individuals or achieved the maximum generation, then the course halts, else, continues.

Step3. Identify Phase:

Step3.1. Compute the affinity of each individual in A_0;

Step3.2. Sort all the individuals by their ascending affinities, then get $A_t=\{a_1,a_2,\Lambda\ ,a_n\}$.

Step4. Active phase:

Divide A_t into $A_t^1=\{a_1,a_2,\Lambda\ ,a_k\}$ and $A_t^2=\{a_{k+1},a_{k+2},\Lambda\ ,a_n\}$, namely $A_t=A_t^1\ \mathrm{Y}\ A_t^2$.

Where k is the active variable, $A_t^1=\{a_1,a_2,\Lambda\ ,a_k\}$ is a cleave set, $A_t^2=\{a_{k+1},a_{k+2},\Lambda\ ,a_n\}$ is a bind set.

Step5. For each individual $a_i(i\in\{1,2,...,k\})$ of A_t^1, execute $O_C(a_i)$ and get a remainder cleave set $(a_{1j},a_{2j},\Lambda\ ,a_{kj})(j=\{1,2\})$, then execute $O_{PB}(a_{1j},a_{2j},\Lambda\ ,a_{kj})$, finally get an individual b_t.

Step6. Membrane attack process:

Step6.1. Bind b_t and each individual of A_t^2, namely $O_{RB}(b_t,a_i)(i\in\{k+1,k+2,\Lambda\ ,n\})$, then get a membrane attack complex set $C_t=\{c_1,c_2,...,c_{n-k}\}$ ($c_i=O_{RB}(b_t,a_i)$, $i\in\{1,2,\Lambda\ ,n-k\}$);

Step6.2. For each c_i of C_t, recode it by the code length of initial individual, then gets a new set $C'=\{c'_1,c'_2,\Lambda\ ,c'_{n-k}\}$.

Step7. Create a random population of complement individuals $D=\{d_1,d_2,\Lambda\ ,d_k\}$, then join them into $C'=\{c'_1,c'_2,\Lambda\ ,c'_{n-k}\}$, finally form a new set $E=C'\ \mathrm{Y}\ D=\{c'_1,c'_2,\Lambda\ ,c'_{n-k},d_1,d_2,\Lambda\ ,d_k\}$.

Step8. $t=t+1$, Go to Step2

ICA has the following characters:

(i)It simulates the classical pathway of the complement system.

(ii)The cleave operator and bind operator can accelerate the convergence of the algorithm through reserving the individual with high affinity in the next generation population.

(iii) There are little manual parameters, which makes the algorithm executed automatically.

5. Experiments and Analysis

The experiment function is following:

$$f(x)=x+10*\sin(5x)+7*\cos(4x),x\in[0,9]. \quad (4)$$

The following parameters are used for the experiments: the initial population size (n) is 50, the initial code length is 10, and the number of generations is 50.

5.1 Experiment 1. The Comparison of ICA with different k.

In the experiment 1, k is 10(20% of n), 25(50% of n) and 40(90% of n) respectively. The result of the experiment is showed in the figure 2.

From the figure 2, we see that the more k is, the quicker the convergence is. When k is 10, the convergence generation is about 15, when k is 25, the

convergence generation is about 6, while k is 40, the convergence generation is about 2.Generally, we suggest that k is equal to 50%-90% of the initial population size.

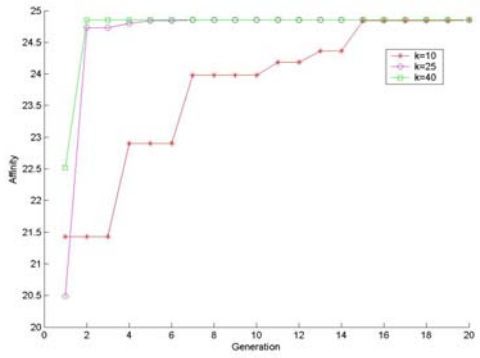

Fig.2 The experiment of ICA with k=10, 25 and 40.

5.2. Experiment 2.The Comparison of ICA with standard genetic algorithm (SGA) .

In the experiment 2, we compare ICA with SGA. In SGA, the crossover probability is 0.95, the mutation probability is 0.08.In ICA, k is 25, P_c is a random number of [0, 1]. The result of the experiment is showed in the figure 3.

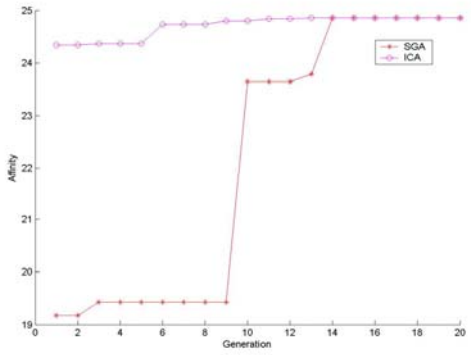

Fig.3 The experiment of SGA and ICA.

From the figure 3, we see that ICA is better than SGA.SGA may converge to the maximum value at 14th generation, while ICA may do only 6th generation.

5.3 Experiment 3.The Comparison of ICA with clonal selection algorithm (CSA).

In the experiment 3, we compare ICA with CSA. In CSA, the select probability is 0.3, mutation probability is 0.1, the clone size is 50.In ICA, k is 40, P_c is also a random number of [0, 1]. The result of the experiment is showed in the figure 4.

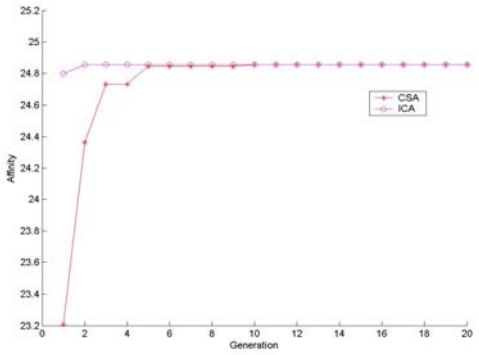

Fig.4 The experiment of CSA and ICA.

From the figure 4, we see that ICA is also better than CSA. CSA may converge to the maximum at 10th generation, while ICA is only 2nd generation.

6. Conclusions and Future Work

In this paper, we develop a novel immunological algorithm based on the complement system-An Immune Complement Algorithm (ICA). ICA mainly simulates the classical pathway of the complement system. In this algorithm, two operators: cleave operator and bind operator are presented, cleave operator cleaves a complement individual into two sub-individual, while bind operator binds two individuals together and forms a big individual .The experiments of compared with the standard genetic algorithm and clonal selection algorithm are implemented. The results show that ICA is better than the standard genetic algorithm and the clonal selection algorithm.

With regard to future perspectives, it may be worthwhile to investigate the following issues:

(i) Comparative studies should also be performed on the basis of other test problems with different characteristics (e.g., non-convexity).

(ii) If possible, other probabilistic search algorithms like simulated annealing, hill climbing, tabu search, etc., as well as “exact” methods (e.g., integer linear programming, branch-and-bound) and deterministic heuristics should be tested.

(iii) The convergence principles of ICA should be discussed. It can offer some theory principles using ICA.

Acknowledgment

This work is supported by the National Natural Science Foundation of China under Grant No. 60575046 and the Science and Technology Foundation of China University

of Mining and Technology under Grant No.E200412 and 2005B008.

References

[1] Leandro Nunes de Castro, Fernando José Von Zuben, "Artificial Immune Systems: Part I – Basic Theory and Applications, "Technical Report, RT–DCA 01/99, December 1999.
[2] L.N.De Castro, F.J.Von Zuben, "the Clonal Selection Algorithm with Engineering Applications," In Proceedings of GECCO'00 Las Vegas, Nevada, USA, 2000.
[3] Jwenw N K, "Towards a Network Theory of the Immune System," Annual Immunology, vol.125c, 1974.
[4] J.Timmis, M.Neal, J.Hunt. "An Artificial Immune System for Data Analysis," Biosystems, vol.55 (1/3), 2000.
[5] Leandro N, de Castro, Fernando J, and Von Zuben, "AiNet: an Artificial Immune Network for Data Analysis," International Journal of Computation Intelligence and Application (IJCIA), vol.1 (3). 2001.
[6] P.D'haeseleer, S.Forrest, "An Immunological Approach to Change Detection: Algorithm, Analysis and Implication," In Proc. of IEEE Symposium on Research in Security and Privacy, Oakland, CA, 1996.
[7] Leandro Nunes de Castro, Fernando José Von Zuben, " Artificial Immune Systems: Part II – A Survey of Applications",TechnicalReport, DCA–RT,021/00,February, 2000.
[8] Michael C Carroll, "The Complement System in Regulation of Adaptive Immunity," NATURE IMMUNOLOGY, Volume 5, Number 10, October 2004.

Chen Guangzhu received the B.E.degree from China University of Mining and Technology in1996. He is a doctoral student at Sichuan Univ. His research interest includes Multi-agent system, intelligent computing and conceptual design.

Li Zhishu received the B.E. and M. E. degrees from Sichuan Univ. in 1969, 1981, respectively. He is a professor at Sichuan Univ. His research interest includes network computing, information systems and intelligent computing.

Yuan Daohua received the B.E. and M.E. degrees, from Nanjing Univ. in 1983 and 1986, respectively. After working as a lecturer (from 1988), and an associate professor (from 1994), he has been a professor at Sichuan Univ. since 1999. His research interest includes distributed parallel processing, network computing, mobile computing, and information systems.