Plasma Cell Negative Regulation Mechanism Based Artificial Immune System

Xishuang Dong, Yi Guan, Jinfeng Yang
Web Intelligence Lab, Research Center of Language Technology, School of Computer Science and Technology
Harbin Institute of Technology
Harbin, China, 150001
dongxishuang@gmail.com, guanyi@hit.edu.cn, yangjinfeng2010@gmail.com

***Abstract*—Plasma cell negative regulation mechanism is taken to construct an artificial immune system by complex system modeling, which is to complete immune theories of existing artificial immune systems. The system consists of immune cell agents such as B cell agents, T cell agents, memory B cell agents, and plasma cell agents and molecular agents such as antigen agents and antibody agents who can interact with each other to simulate adaptive immune responses. Moreover, T cell agents can be killed through being bound by plasma cell agents specifically, which is to simulate the process of the plasma cell negative regulation. Experimental results show that not only adaptive immune responses can be simulated by the system, but also the efficiency of primary immune responses can be improved under the effect of that mechanism.**

Keywords-plasma cells; adaptive immune theories; artificial immune system; complex sytem modeling

I. INTRODUCTION

Artificial immune systems (AIS) based on complex system modeling (CSM) [1, 2, 3, 4] can help us understand behaviors of immune cells and molecular and validate immune theories. Firstly, experimental processes simulated by AIS can be observed and monitored conveniently. On the contrary, experiments on animals consume large amounts of financial and material resources, and it's impossible to perform systematic tests in humans. Secondly, new immune theories can be integrated easily into AIS to test its effectiveness. However, there are only three immune theories namely, clonal selection, negative selection, and idiotypic immune network in present AIS. We adopt the plasma cell negative regulation mechanism (PCNRM) to complete immune theories of the present AIS in order to achieve more realistic simulations of immune responses.

In 2010, Pelletier [5] present the plasma negative regulation mechanism. Plasma cells not only compound, store, and secrete a large number of antibodies with high affinities to kill antigens, but also bind Th cells to suppress the diversity of the population of Th cells, which is to improve the efficiency of adaptive immune responses. Therefore, we integrate the mechanism into the existing AIS to construct a new artificial immune system, which is to realize the more accurate simulation of the immune responses and theories.

The system is constructed by CSM, where immune cells and molecular are built as independent agents. These agents consist of cell agents (B cell agents, T cell agents, plasma cell agents, memory B cell agents, and self cell agents) and molecular agents (antigen agents and antibody agents) whom are built through simulating receptors, behaviors, and states of cells and molecular involved in adaptive immune responses. Immune theories simulated in the system include negative selection, clonal selection, idiotypic immune network, and PCNRM. Experimental results show that not only adaptive immune responses can be simulated by the system, but also PCNRM can be used to improve the efficiency of primary immune responses actually.

The remainder of the paper is organized as follows. In section two, we summarize researches of immune theories and AIS. An artificial immune system based on PCNRM is constructed in detail in section three. In section four, experimental results are shown and analyzed. Finally, we outline conclusions.

II. RELATED WORK

An overview of immune theories and AIS is given in this section. Immune theories include negative selection (NS) theory, idiotypic immune network (IIN) theory, and clonal selection (CS) theory. NS theory refers to that T cells bound by self cells with high affinities are eliminated so as to protect bodies from attracting by T cells [6, 7], and people construct negative selection algorithms based on NS theory to solve problems such as the partition of software and hardware in embedded systems [8], aircraft fault detection [9], and motor abnormal detection [10]. Jerne presented IIN theory indicating that B cells or antibodies can form a network by stimulus and suppression so as to realize the function of immunological memory [11], and IIN algorithms can be applied to clustering, data visualization, and automatic control [12]. CS theory refers to that B cells stimulated by antigens and T cells specifically can mutate to generate new B cells with higher affinities that can differentiate memory B cells and plasma cells, where plasma cells can secret antibodies to kill antigens [13]. Algorithms based on CS theory can be applied to function optimization [14], pattern recognition [15], job and project scheduling [16, 17], and TSP [18].

In the respect of AIS, all simulation systems are constructed based on these theories. In addition, methods to constructing AIS are based on agents and cellular automata. The first artificial immune system based on agents and cellular automata is built by Celada-Seiden to simulate humoral responses, where the focus is on simulating the

processes of binding antigens in adaptive immune responses. Then, ImmSim was presented based on probabilistic rules to reproduce and analyze immunological memory, affinity maturation, effects of hypermutation, autoimmune responses, and competitive tolerance [19]. To improve the efficiencies of simulations, people present C-ImmSim and ParImm [20, 21]. Moreover, Nicolas provided an online C-ImmSim, where the computation of affinities was improved by Parker-scale affinity estimation [22]. And Touraj Banirostam presented an artificial immune system based on Capra Cognitive Framework [23]. These systems can be applied to simulating interactions among cells and molecular in the process of HIV [24], cancer [25], and virus infection [26]. And Rapin N combined machine learning methods with artificial immune systems to realize prediction of communications between immune agents [27]. On the other hand, Virginia adopted a multi-agent artificial immune system to analyze communications in the complex immune network [28]. However, these systems usually contain three immune theories mentioned above. We construct an artificial immune system based on PCNRM to complete immune theories.

III. ARTIFICIAL IMMUNE SYSTEM MODELING

The system consists of key elements (B cell agents, memory B cell agents, plasma cell agents, antigen agents, and antibody agents) and auxiliary elements (T cell agents and self cell agents), where system flows are realized by interactions between elements.

A. System Flows

System flows are shown in Fig. 1.

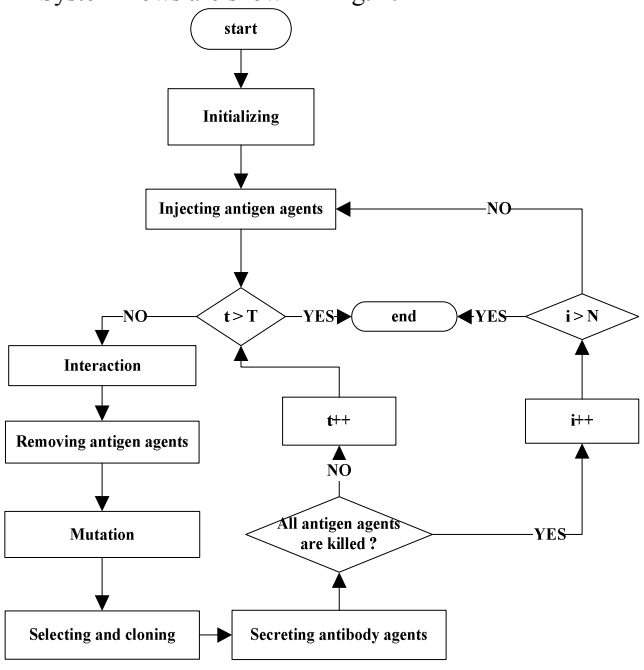

Figure 1. System flows

where i denotes times of injecting antigen agents into the system, and t denotes times of running the system flows. And N denotes the threshold of times of injecting antigen agents, and T denotes the threshold of times of running. There are six steps in these flows: (1) Initializing. When the system is initialized, receptors and numbers of B cell agents, T cell agents, and self cell agents are initialized. And, under the effect of the NS theory, T cell agents bound to self cell agents with high affinities are selected to be removed. Meanwhile, parameters of the system such as the mutation possibility threshold and numbers of agents are initialized; (2) Injecting antigen agents. Antigen agents are injected into the system; (3) Interaction. Interactions between agents are realized under theories such as CS, IIN, and PCNRM; (4) Removing antigen agents. Antigen agents killed by antibody agents or B cell agents are removed from the system in the process of removing antigen agents; (5) Mutation, selecting, and cloning. B cell agents bound to antigen agents can mutate with high possibilities to generate new B cell agents with higher affinities. And these new B cell agents are selected to clone and differentiate memory B cell agents and plasma cell agents; (6) Secreting antibody agents. These plasma cell agents secret antibody agents to kill antigen agents specifically. If all antigen agents are not killed and the time of running is less than the threshold T, then repeat (3) to (6). If all antigen agents are killed and the time of injecting antigen agents is less than the threshold N, then repeat (2) to (6). If the time of running is more than the threshold T, or the time of injecting antigen agents is more than the threshold N, then the running of the system flows is terminated. These flows are run based on immune agents as follows.

B. Immune agents

Immune agents are composed of immune cell agents including B cell agents, T cell agents, self cell agents, memory B cell agents, plasma cell agents, and immune molecular agents including antigen agents and antibody agents.

The B cell agent is constructed by simulating receptors, states, and behaviors of B cells, and the state transaction is realized through running behaviors selected according to the current state. Receptors of B cell agents are constructed as shown in Fig. 2.

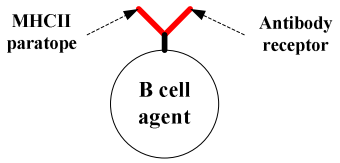

Figure 2. Receptors of B cell agents

The agents have two receptors namely Major Histocompatibility Complex (MHC) II paratope and antibody receptor. The paratope can be bound to receptors of T cell agents specifically, while the antibody receptor can be bound to receptors of antigen agents. These two receptors are constructed by generating binary strings randomly. Affinity can be used to measure the matching degree between receptors. When matching receptors, it assumes that the

higher the bit in the receptor is, the larger the weight is. The matching degree is calculated as equation (1).

$$F_{match} = (1+\alpha)\times\sum_{i=1}^{M}\frac{i}{M}\times a_i - \sum_{j=1}^{M}\frac{j}{M}\cdot 1 \quad (1)$$

where α is the matched factor. a_i denotes whether the ith bit is matched or not. If the ith bit is matched, the value of a_i is set 1, otherwise 0. M is the length of the receptor. All lengths of receptors are the same. It assumes that there is the exponential relationship between the affinity and the matching degree. The affinity is calculated as equation (2).

$$F_{affinity} = \sqrt{\frac{F_{match}\times e^{F_{match}}}{factor}} \quad (2)$$

where the factor denotes the affinity factor. States of B cell agents include active, bound, mutated, duplicated, and anergic states. And the state transaction is constructed based on the CS theory. Active state is the initial state. Active B cell agents can move freely and perceive antigen agents. Their states can become bound when running the matching behavior that the antibody receptor of B cell agents can be matched with receptors of antigen agents specifically. Then, bound B cell agents become mutated by binding receptors of active T cell agents with the paratope, and they run the mutating behavior as algorithm 1, where $v_{receptor}$ denotes receptors, and *mutatePro* denotes the threshold of mutation of receptors.

Algorithm 1 Mutation

Input: $v_{receptor}$
Output: $v'_{receptor}$
Set the value of *mutatePro*;
for each of bit $v_{receptor}[i]$
  Generating the random possibility p_{rand};
  if p_{rand} < *mutatePro*
    $v'_{receptor}[i] = 1 - v_{receptor}[i]$;
  end if
end for

B cell agents with higher affinities will be generated through the mutating behavior and become duplicated. The duplicated B cell agents will differentiate memory B cell agents and plasma cell agents and become active. In addition, each active B cell agent will become anergic at a certain probability so that the agents cannot interact with other agents. On the other hand, the anergic B cell agents will become active at a certain probability. One of differences between B cell agents and the rest of immune agents is that the rest of immune agents only have one receptor.

T cell agents are constructed through simulating receptors, behaviors, and states of Th cells. Their receptors can be matched with receptors of plasma cell agents and the paratope of B cell agents. Their states include active, duplicated, and dead states. Active T cell agents can move freely and perceive immune cell agents and molecular agents. If they perceive B cell agents and the affinities between the paratope and the receptor of T cell agents are larger than the affinity threshold, their states become duplicated. The duplicated T cell agents will clone many T cell agents. On the other hand, if they perceive plasma cell agents, and the affinities between their receptors and receptors of plasma cell agents are larger than the affinity threshold, states of the T cell agents and plasma cell agents become dead. In addition, states of active self cell agents and T cell agents will become dead when they are bound to each other.

As mentioned above, the duplicated B cell agents will differentiate plasma cell agents and memory B cell agents. Plasma cell agents' receptors can be matched with receptors of T cell agents. States include active and dead states. Active plasma cell agents encounter active T cell agents, and if the affinity between receptors is larger than the affinity threshold, the state of plasma cell agents and T cell agents are set dead to suppress the population of T cell agents, which is to simulate the process of the plasma cell negative regulation. And plasma cell agents can secrete antibody agents to kill antigen agents. Memory B cell agents' receptors can be matched with receptors of antigen agents. And if the affinity of receptors is larger than the affinity threshold, memory B cell agents differentiate plasma cell agents that can secrete antibody agents to kill antigen agents and become dead.

Immune molecular agents include antigen agents and antibody agents. Active antigen agents can be bound to B cell agents, memory B cell agents, or antibody agents to become dead. Active antibody agents can be bound to B cell agents under the effect of IIN theory, or antigen agents to become dead. Simulations of immune responses are realized by interactions between immune agents. In next section, we introduce and analyze experimental results.

IV. EXPERIMENT AND ANALYSIS

Experiments contain two parts. In the first part, through simulation experiments, we check whether the system can be used to simulate adaptive immune responses or not, where the same number of antigen agents is injected into the system twice for simulating the primary response and the second response respectively. In the second part, through comparing the system with the artificial immune system that does not contain the PCNRM, we check whether efficiencies of adaptive immune responses can be improved or not.

A. Simulation results of adaptive immune responses

Main parameters of the system are initialized as TABLE I.

TABLE I. SYSTEM PARAMETERS

Name of parameters	Values
Number of B cell agents	130000
Number of T cell agents	390000
Number of antigen agents	1000
Receptor of antigen agents	41
Threshold of times of running	10000
Min-match bit	17
Length of receptors	22

where the Min-match bit denotes the minimum number of bits of matching receptors. Experimental results are shown in Fig. 3, where x-axis denotes times of running, and y-axis denotes numbers of antigen agents.

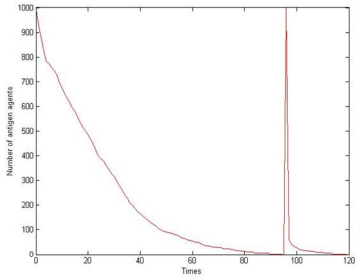

Figure 3. Number changes of antigen agents in adaptive immune responses

The reduced speed of numbers of antigen agents in the second response is much faster than that in the primary response because in the second response there are a large quantity of antibody agents secreted by plasma cell agents to kill antigen agents, while in the primary response there are only B cell agents and a small quantity of antibody agents, which reflects the main property of adaptive immune responses.

In addition, we compare results conducted with different values of min-match bit as shown in Fig. 4.

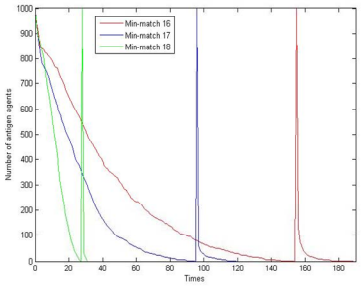

Figure 4. Number changes of antigen agents with different values of min-match

Different values of min-match bit lead to different efficiencies of immune responses, where the larger the value of min-bit is, the higher the efficiency is. On the other hand, we compare results conducted with different lengths of receptors as shown in Fig. 5.

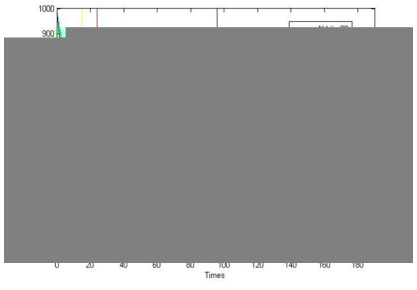

Figure 5. Number changes of antigen agents with different lengths of receptors.

The smaller the length of receptors is, the higher the efficiency of immune responses is. But when the length of receptors is larger than a threshold, the efficiency is increased suddenly. For example, when the length of receptors is 26, the efficiency is the highest. From the Fig. 4 and Fig. 5, we find that simulation results are sensitive to parameter values of the system. In addition, through comparison experiments, we check whether efficiencies of adaptive immune responses can be improved under the effect of PCNRM.

B. Results of comparison experiments

The system parameters are set as TABLE II.

TABLE II. SYSTEM PARAMETERS

Name of parameters	Values
Number of B cell agents	130000
Number of T cell agents	390000
Number of antigen agents	1000
Receptor of antigen agents	41
Threshold of times of running	10000
Min-match bit	18
Length of receptors	22

The system compared is an artificial immune system that does not contain the PCNRM, but contains CS theory, IIN theory, and NS theory. Experimental results are shown in Fig. 6.

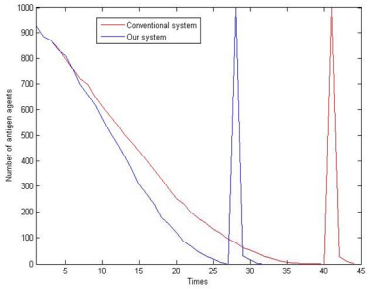

Figure 6. Results of the comparison experiment

Times of primary immune responses in our system are much less than those in the system compared, which means that the efficiency of primary immune responses can be improved under the PCNRM

V. CONLCUSIONS

We present the PCNRM based artificial immune system. The system is a multi-agent complex system composed of main immune cell agents and immune molecular agents involved in adaptive immune responses. Experimental results show that the system can be used to simulate adaptive immune responses, and under the effect of PCNRM, efficiencies of primary immune responses are improved. But simulation results are sensitive to values of system parameters. The future work is that we will integrate

more immune theories into the system such as the danger theory.

ACKNOWLEDGMENT

This work was supported by National Natural Science Foundation of China (Project No. 60975077).

REFERENCES

[1] Fachada, N. "SimulIm: an application for the modeling and simulation of complex systems, using the immune system as an example," Graduation project report, Instituto Superior Tcnico, Universidade Tcnica de Lisboa, 2005.

[2] Celada, F., and Seiden, P. "A computer model of cellular interactions in the immune system," Immunology Today, vol.13, 1992, pp.56-62.

[3] Seiden, P., and Celada, F. "A model for simulating cognate recognition and response in the immune system," J Theor Biol, vol. 158, 1992, pp. 329–357.

[4] Kleinstein, S., and Seiden, P. "Simulating the immune system," Computing in Science and Engineering, vol. 2, 2000, pp. 69–77.

[5] Nadege Pelletier, Louise J. McHeyzer-Williams, Kurt A. Wong, Eduard Urich, Nicolas Fazilleau, and Michael G. McHeyzer-Williams. "Plasma Cells Negatively Regulate the Follicular Helper T cell Program," Nature Immunology, vol.11, 2010, pp. 1110–1118.

[6] Stephanie Forrest, Alan S. Perelson, Lawrence Allen, and Rajesh Cherukuri. "Self-nonself Discrimination in a Computer," In Proceedings of the 1994 IEEE Symposium on Research in Security and Privacy, 1994, pp. 202–212.

[7] Dasgupta D and Forrest S. "An Anomaly Detection Algorithm Inspired by the Immune System," Artificial Immune System and Their Applications, vol.57, 1999, pp. 262–277.

[8] Yiguo Zhang, Wenjian Luo, Zeming Zhang, Bin Li, and Xufa Wang. "A Hardware/Software Partitioning Algorithm based on Artificial Immune Principles," Applied Soft Computing, 2008, pp. 383–391.

[9] D. Dasgupta, K. KrishnaKumar, D. Wong, and M. Berry. "Negative Selection Algorithm for Aircraft Fault Detection," In G. Nicosia et al. (Eds), Proceedings of Third International Conference on Artificial Immune Systems (ICARIS 2004), 2004, pp. 1–13.

[10] Gan Z, Zhao M B, and Chow T W S. "Induction Machine Fault Detection Using Clone Selection Programming," Expert System with Applications, vol. 34, 2009, pp. 8000–8012.

[11] Jerne N K. "Towards a network theory of the immune system," Annales dimmunologie, vol. 125C (1- 2), 1974, pp. 373–389.

[12] Guilherme Palermo Coelho, and Fernando J. Von Zuben. "A Concentration-Based Artificial Immune Network for Multi-objective Optimization," Evolutionary Multi-Criterion Optimization, vol. 6576, 2011, pp. 343–357.

[13] Gong M, Jiao L, Yang J, and Liu F. "Lamarckian Learning in Clonal Selection Algorithm for Numerical Optimization," International Journal on Artificial Intelligence Tools, vol. 19, 2010, pp. 19–37.

[14] Jin-hui Yang, Liang Sun, Heow Pueh Lee, Yun Qian, and Yan-chun Liang. "Clonal Selection based Memetic Algorithm for Job Shop Scheduling Problems," Journal of Bionic Engineering, vol. 5, 2008, pp.111–119.

[15] Garain U, ChakrabortyMP, and Dasgupta D. "Recognition of Handwritten Indict Script Using Clonal Selection Algorithm," In Proceedings of the 5th international conference on Artificial Immune Systems (ICARIS' 06), 2006, pp. 256–266.

[16] Moghaddam M Z and Kardan A. "Clonal Selection Algorithm for Partitioning and Scheduling of Codesign Systems," In 5th International colloquium on signal processing and its applications, 2009, pp. 267–272.

[17] Li D and Chen Z. "SVM Optimized by Immune Clonal Selection Algorithm for Fault Diagnostics," In Proceedings Pacific-Asia conference on circuits, communications and systems (PACCS 2009), 2009, pp. 702–705.

[18] Yong L and Sunjun L. "A Hybrid Model for Solving TSP based on Artificial Immune and Ant Colony," In International conference on information engineering and computer science (ICIECS 2009), 2009, pp. 605–609.

[19] Puzone, R., Kohler, B., Seiden, P., and Celada, F. "IMMSIM, a flexible model for in machina experiments on immune system responses," Future Generation Computer Systems, vol. 18, 2002, pp. 961–972.

[20] M. Bernaschi, and F.Castiglione. "Design and implementation of an immune system simulator," Computers in Biology and Medicine, vol. 31, 2001, pp. 303–313.

[21] Baldazzi, V., Castiglione, F., and Bernaschi, M. "An enhanced agent based model of the immune system response," Cellular Immunology, vol.244, 2006, pp. 77–79.

[22] Rapin Nicolas, Lund Ole, and Castiglione Filippo. "Immune system simulation online," Bioinformatics, vol. 27, 2011, pp. 2013–2014.

[23] Touraj Banirostam and Mehdi N. Fesharaki. "Immune System Simulation with Biological Agent Based on Capra Cognitive Framework," 2011 13th International Conference on Modelling and Simulation, 2011, pp.122–127.

[24] Castiglione, F. and Bernaschi, M. "HIV-1 Strategies of Immune Evasion," International Journal of Modern Physics C, vol. 16, 2005, pp. 1869–1878.

[25] Motta, S., Castiglione, F., Lollini, P., and Pappalardo, F. "Modelling vaccination schedules for a cancer immunoprevention vaccine," Immunome Research,vol. 1, 2005.

[26] Castiglione, F., Duca, K., Jarrah, A., Laubenbacher, R., Hochberg, D., and Thorley- Lawson, D. "Simulating Epstein-Barr Virus Infection with C-ImmSim," Bioinformatics, vol. 23, 2007, pp. 1371–1377.

[27] Rapin N, Lund O, Bernaschi M, and Castiglione F. "Computational Immunology Meets Bioinformatics: The Use of Prediction Tools for Molecular Binding in the Simulation of the Immune System," PLoS ONE, vol. 5, 2010.

[28] Virginia A Folcik, Gordon Broderick, Shunmugam Mohan, Brian Block, Chirantan Ekbote, John Doolittle, et al. "Using an agent-based model to analyze the dynamic communication network of the immune response," Theoretical Biology and Medical Modelling, 2011.