# 4. Designing Artificial Immune System Based on Clonal Selection Using Agent-Based Modeling Approach

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# Asia Modelling Symposium 2013

## Seventh Asia International Conference on Mathematical Modelling and Computer Simulation

## AMS 2013

23 July 2013, Hong Kong
25 July 2013, Kuala Lumpur, Malaysia

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# Welcome Message from the Chairs

# AMS 2013

We are very pleased to welcome our colleagues from Asia and other parts of the world to the Asia Modelling Symposium 2013 (AMS 2013), the seventh Asia international conference on mathematical modelling and computer simulation, held at two locations: day-1 in Hong Kong on 23 July and day-2 in Kuala Lumpur, Malaysia, on 25 July. The conference Program Committee has organized an exciting and balanced program comprising presentations from distinguished experts in the field, and important and wide-ranging contributions on state-of-the-art research that provides new insights into the latest innovations in the mathematical and analytical modelling and computer simulation of a diverse range of topics in science, engineering and technology focused on intelligent systems. The seventh such event in this region, it follows in the foot steps of the sixth Asia international conference on mathematical modelling and computer simulation, held at two locations: day-1 in Kuala Lumpur, Malaysia, on 28 May and day-2 in Bali, Indonesia on 31 May 2012, the fifth event held in Kuala Lumpur and Manila in May 2011, the forth held in Kota Kinabalu, Malaysia in May 2010, the third held at two locations in Indonesia, Bandung and Bali, in May 2009, the second held in Kuala Lumpur in May 2008, and the first held jointly with the 11th Thai Annual National Symposium for Computational Science and Engineering, ANSCSE-11, in March 2007 at the Prince of Songkla University campus in Phuket. We are hopeful that its outstanding technical content contributed by leading researchers in the field from Asia and worldwide will ensure its continued success. No plans have yet been finalized for the location of next year's event, but it would be appropriate to choose another interesting location in a neighboring country in south east Asia.

The main themes addressed by this conference are:

Fuzzy Systems
Evolutionary Computation
Bioinformatics and Bioengineering
Emergent Technologies
Intelligent Systems and Applications
Hybrid and Soft Computing
Robotics, Cybernetics, Engineering, Manufacturing and Control
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countries. The conference program committee had a very challenging task of choosing high quality submissions. Each paper was peer reviewed by several independent referees of the program committee and, based on the recommendation of the reviewers, 51 papers were finally accepted for publication. The papers offer stimulating insights into emerging modelling and simulation techniques for intelligent and hybrid intelligent systems and systems that employ intelligent methodologies. We express our sincere thanks to the keynote and tutorial speakers, authors, track chairs, program committee members, and additional reviewers who have made this conference a success. Finally, we hope that you will find the conference to be a valuable resource in your professional, research, and educational activities whether you are a student, an academic researcher, or a practicing professional. Enjoy!

**David Al-Dabass, Yiu-ming Cheung, Hong Jia, Zuwairie Ibrahim, Jasmy Yunus,**
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# Designing Artificial Immune System Based on Clonal Selection

## Using Agent-Based Modeling Approach

Ayi Purbasari[#1], Iping Supriana S[#2], Oerip S. Santoso[#3], Rila Mandala[#4]
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***Abstract*— Bio-inspired computing is the idea to emulate and to get inspirations from biological systems which is then used to solve complex problems. Artificial immune systems, as one of the bio-inspired computing has contributed in solving complex problems. From one generation to another generation, AIS's practitioners realize that to get better algorithms we need the inspiration with the better understanding about the behavior of the immune system. Modeling is the key to get better understanding and inspiration from immune system. Agent-based modeling can be used because of the components of the immune system can be described as agents that interact with each other and set up a system behavior. There are two approaches to agent-based modeling, i.e. modeling of the immune system itself and model the artificial immune system. In this paper we design a model for immune system using agent-based approach. This model specifically based on clonal selection and its behavior. The design of model are using UML diagram to describe the behavior and the interaction of agents. This design can be used for simulating existing artificial immune system models, developing new artificial immune system models, or evaluating artificial immune system models that have been already adapted to technical problems.**

***Keywords- Artificial Immune System; Agent-based Modeling; Clonal Selection***

## I. INTRODUCTION

Bio-inspired are known as techniques to improve computational techniques by mimicking natural system and achieving similar desirable properties of the natural system. A famous bio-inspired is neural networks and so is genetic algorithms. Based on metaphor and abstraction from theoretical of the vertebrate immune system, there are Artificial immune systems (AIS) as another promosing biological inspired computation. Artificial immune systems (AIS) simulate the behavior the natural immune system. Artificial Immune Systems (AIS) are algorithms and systems that use the human immune system as inspiration and have been used to solve some engineering problems. Some properties of human immune system are highly desirable for novel computer systems development. Unlike genetic algorithms and neural networks, the field of AIS encompasses a spectrum of algorithms that exist inspired by the behaviour and properties of immunological cells, specifically B-cells, T-cells and dendritic cells (DCs). AIS have been developed three algorithms derived from more simplified models:clonal selection, negative selection, and immune networks. However, these first-generation AIS algorithms have often shown considerable limitations when applied to realistic applications [1]. For this reason, a second generation of AIS is emerging, using models derived from cutting-edge immunology as their basis, not simply mechanisms derived from basic models. For this way, modeling is important in Artificial Immune System.

Stepney et. all [2] presented the conceptual framework for AIS, showing that modelling in AIS plays an important role in the understanding of the immune system computational aspect. Modeling approach in AIS is operating at different levels of abstraction.There is a vast range of modeling approaches available, from mathematical modeling to object oriented modeling approach. Modeling will help us to understand how the immune system compute from computational dan engineering perspectives.

Agent based modeling approach is believed as an approach that fit in for this requirement. An agent represents an immune system cell and they collaboratively show the emergence behavior of immune system.

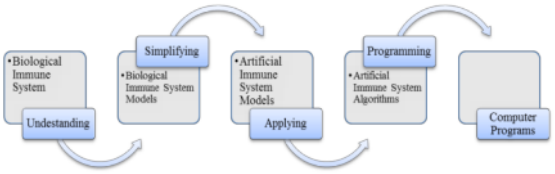



Figure 1 Artificial immune systems flow

As we can see in figure of Artificial Immune Systems flow above, there are two kind of modeling based on agent [3]: 1) modeling for IS itself and 2) modeling for AIS. Some recent works show the valuable work in IS modeling and AIS modeling using agent based. But we have not a work for clonal selection modeling using agent based. While clonal selection is the most important concept from IS, we need better understanding about it. In this paper we summarize several recent examples of work that has been done in immune modeling and explore specific examples of

clonal selection models based on agent that can be used to understand the dynamics of clonal selection concept.

## II. METHOD AND MATERIAL

### A. *Method*

At first, we study about immune system, clonal selection theory, and agent based modeling. Then we summarize several examples of work that has been done in immune modeling using agent based approach. At last, we design agent-based model for Artificial Immune System, especially for clonal selection behavior. This method can be seen at thefigure 2 below:


Figure 2 Method for Clonal selection agent-based modeling

### B. *Immune Systems and Clonal Selection Theory*

The immune system consists of more than 15% of genes in the human genome, that is why immune function plays a vital role in human health [7]. The immune system protects human health against external invaders, such as viruses, bacteria, and other pathogens, while ignoring self. The immune system has mechanisms to discriminate between self and nonself that are becoming elucidated, but are far from being completely understood. The most immune decisions e.g., whether to attack or tolerate a certain target, or whether to magnify or suppress an immune response are not made autonomously by individual cells or even by a few isolated cells. Most immune responses result from interactions among various types of cells, continually signaling to one another via their mechanisms. Most immune has additional regulatory mechanisms results from different states (resting/active, immature/mature, naive/effector/memory) of their cells. There are two kind of immune responses, innate immune response and acquired immune responses [4]. As AIS are inspired from acquired immune response, this paper will describe how this mechanism works.

Here is the description of the acquired immune response [4]:

1) Typically, the immune response is activated when a pathogen enters the body. Macrophages detect pathogens, ingest them and broke down into fragments, and display the antigen fragment on their cell surfaces. This is called antigen-presenting cells, and a T Helper Cell will interact with APC to recognize the antigen.
2) The communications between immune cells are via release chemical signals. Macrophages release a chemical alarm signal called Interleukin-1, which stimulates the T Helper Cell to secrete Interleukin-2. Interleukin-2 causes the activation of T Killer Cells and B cells.
3) Since the T Killer Cell and B cells active, there are two paths in immune response, one using T Killer Cells (Cytotoxic T Cells) and the other using B-cells.
4) If the system is using Cytotoxic T Cells, it needs APC displayed on infected cell's surfaces. Infected cells can also digest some of the pathogens and display antigen fragments on their cell surfaces. Then the body makes millions of different type of Cytotoxic T Cells (CTLs), each type is able to recognize a particular antigen. They are capable of recognizing the antigen displayed on the surfaces of infected cells, binding to the infected cells, and producing chemicals that kill the infected cell.
5) If the system is using B cells, then the body makes millions of different type of B cells and their spesific receptor. Each B cell is able to recognize a particular antigen. When B-cells recognize a particular antigen, B cells become activate (they're also helped by T Helper Cells), then they clone theirself into several B-cells with same receptor. The clones then differentiate into plasma cells that secrete antibodies flooding the bloodstream. These antibodies are binding to the antigen on the surfaces of the pathogens, marking them for ingestion by macrophages. Some of the B cells become memory B cells that may live for long life times. These memory B cells make the secondary immune response to a future infection which is swifter and stronger.

B cells clonning mechanism is known as clonal selection and it's based on clonal selection theory proposed by Burnet (1959). This is a theory specifically to describe the diversity of antibodies used defend the organism from invasion. B lymphocyte cells produce antibody uniquely and it's customised to specific type of antigen..

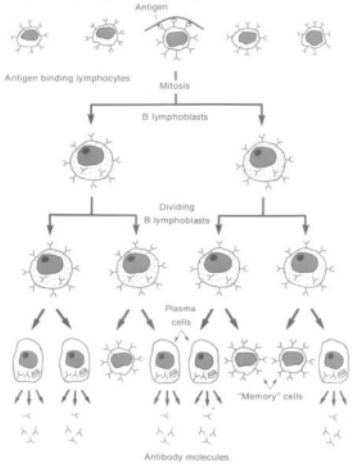



Figure 3 Clonal selection mechanism [5]

Figure 3 above shows the mechanism of antibodies produced as we describe at point 5 above. Here is the detail: 1) B cells that bind to specific antigens. 2) Once bound, B cells proliferates (divideds or mitosis) and produces many B lymphoblasts. 3) B lymphoblasts differentiate into either plasma cells that produce antibodies (effector of the immune

response), 4) Some of B cell become long lived memory cells that can be used if the antigen reappears

During the proliferation stage, genetic mutations called hypermutations occur in the clone of cells that promote the match or affinity with the antigen. This allows the binding ability of the cells to improve with time and exposure to the antigen. This selection of replication cells by antigens can be viewed as a type of Darwinian microcosm where the fittest cells (best match with antigens) are selected for survival, and genetic mutation provides cell variation. The hypermutation process of clonal selection is controlled and directed proportional to the receptors affinity with the triggering antigen.

The immune system has the capability to differentiate between self and non-self, called tolerance. This ability is developed as the immune system itself develops. This ability to not generate antibodies against own cells, can be acquired for foreign antigens that are administered to the organism. Since the antigen is not persistent in the organism, this aspect of tolerance cannot be maintained. The figure 4 provides an additional schematic overview of the clonal selection process and how antigen tolerance is achieved. Here the figure 4 shows the development of B lymphocyte cells and the negative selection against those cells that respond to self or are self-reactive.

Another aspect of the clonal selection theory is that the system has ability to regulae itself. When the system detects and responds to a foreign antigen, it is able to then return to a level of equilibrium.

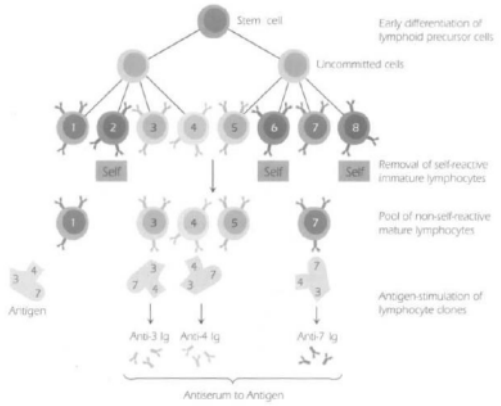



Figure 3 Tolerance in clonal selection [5]

### C. *Agent Based Modelling for Immune System*

An agent is a discrete entity with its own goals and behaviors. It is autonomous, or self-directed, with a capability to adapt and modify its behaviors. Agents are diverse and heterogeneous. Agent-based modeling is a modeling that begins and ends with the agent's perspective. Agent-based modeling models the behavior of populations of components and their interactions within a system [6]. The key of this approach is to model the system components as autonomous agents and to simulate their behavior for evaluating the system as a whole. Agent-based modeling is very useful for observing the emergence of properties in social, environmental, financial systems, or biological, including immune system. An agent-based model consists of – a set of agents, a set of agent relationships, a framework for simulating agent behaviors and interactions. The set of agents and relationships are usually part of the user-defined model and simulation framework is usually provided by provided by an ABMS toolkit or other implementation.

This table below are several ABMs for immune system modeling [6,7,8]:

Table 1. Several ABMs for immune system modeling

| IS modeling | Provided by |
|---|---|
| The interaction between a T cell and a dendritic cell in the lymph node, they obtain estimates of the frequency of T cell–DC interactions and the expected time for T cells to become fully stimulated | Catron et.al., 2004 |
| T cell competition for access to binding sites on mature antigen-bearing APCs | Scherer et al., 2006 |
| B cell migration in the germinal center of a lymph node | Figge et al., 2008 |
| T cell scanning of the surface of an APC | Casal et al., 2005 |
| The interactions between the cells of the innate and adaptive immune system | Folcik et al., 2007 |

There are no agent-based modeling for clonal selection processing in immune system.

Montealegre and Rammig [9] give some hints of how to perform agent-based modeling and simulation of systems, as below:

1) Define the purpose of the model and the output logs to become after simulation,
2) Identify agent/component types within the system and define the attributes for each agent/component type.
3) Identify behavior of the agents in the system for defining the base level decision rules and the high level rules which change the base level decision rules bringing out learning and adaptation,
4) Identify the agent-agent and the agent-environment interactions in the system to be modeled (which agents interact, when they interact and how they interact).
5) Define the type of environment where the agents are going to be placed. The environment can be of one, two or three dimensions visualization.

6) Implementation: Agent-based modeling and simulation can be implemented with software of general use such as: Matlab (using of Simulink and the toolbox SimEvents) or with specialized software for agent-based modeling and simulation such as: Repast, NetLogo, etc. Most of the specialized software available are based on the object oriented paradigm and consider an agent as an object class or object template and its behavior expressed by object methods.
7) Run simulations for different sets of parameters, observing the behavior of each agent (micro level) and the behavior of the whole system (macro level).
8) Robustness of the model: Find out the robustness of the model using sensitivity analysis. The analysis of sensitivity of the model can be executed systematically changing variables in the model for determining the effects of such changes.

## III. RESULT AND DISCUSSION

### A. *Designing Agent Based Modeling for Clonal Selection*

We can use the Unified Modeling Language (UML) for representing agent-based models. UML is a standardised specification language that can be used for general purpose modelling allowing for the creation of an abstract model of the system under study. UML is commonly adopted to support agent-based models in both the design and communication phases. UML consists of a number of high-structured types of diagrams and graphical elements that are assembled in various ways to represent a model. We can user the class diagrams to describe agents within the system, state-chart diagram to describe behavior of the agents, and sequence diagram to describe interaction between agent or between agent-environment.

Section II.C has given a concise set of steps to follow for developing agent-based modeling for any system. using hints from section 2.3, in this section we will design an agent-based modeling for clonal selection. From eight steps, we will describe 5 steps. Here the summary for technique and their steps:

1) Purpose and output

The purpose is to show the clonal selection mechanism under the presence of antigens and the outputs are:

- the dynamics of the population of cells vs number of runs,
- the number of remaining pathogens vs runs
- how effective and fast the clonal selection is.

2) Defines agents

The model considers the bind between actived B-cells and spesific antigen, B-cell cloning and getting hypermutation, and then producing antibodies. Then the agents are: B-cell and antigen. Here the class diagram for describing agents within the system. From all agents/components defined above, we will focus to B cells and exogenous antigens. The attibutes for this models are: present, active, antigen-signature.

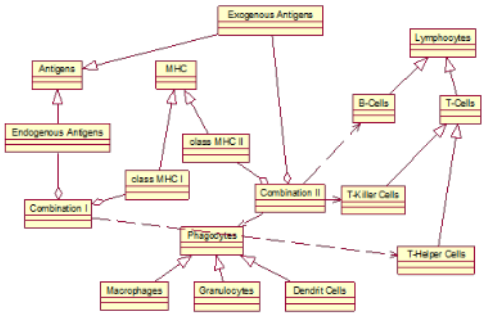
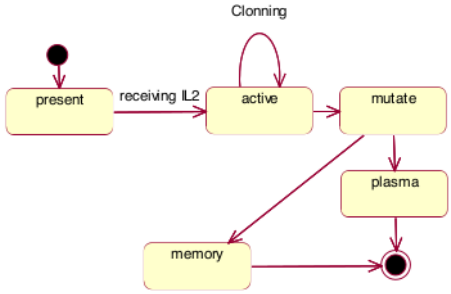



Figure 4 Class diagram for Immune System

3) Define agents behavior

The theory of agent behavior has been presented in section 2 for each immune system cell. Each cell/agent type has behavior: initialization, activation, reproduction/clonning, death. The detail will be describe in figure 6 below.

Figure 5 Behavior of Antigen




4) Define agents interactions

The theory of how the agents interact has also been presented in section 2. From that description and regarding only the adaptive immune response, this simplified model of agent interaction can be abstracted: antigen → macrophage → T-cell → B-cell ← antigen. The detail will be describe in figure 7 below.

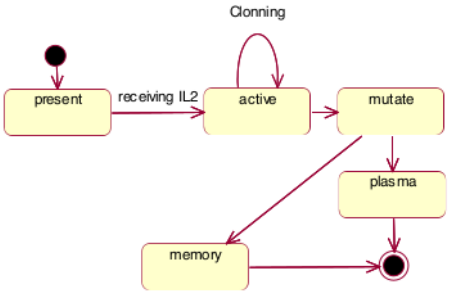



Figure 6 Behavior of B cells

5) Define Environment

The next step is to define the type of environment where the agents are going to be placed. The environment for agent visualization can be of one, two or three dimensions. We will use a one-dimensional network of cells, and for visualization purposes, we will use a two dimensional positioning of the cells/agents.

### *B. Discussion and Future Works*

We have already designed an agent-based modeling for clonal selection. We use UML diagram to help understanding about agents, their behavior, and their interaction. UML helps to visualize the design. .As we can see, the UML digrams are also the model itself but we use them to design an ABM. We can complete and detailing the diagrams to have the more complete ABM.

This paper only describe 5 steps for designing an ABM. So the next works are:

- Implementation ABM into program using software/tools that specific for ABM. We recomend Repast because of there is Java version for Repast in oo paradigms that matched to UML diagram that we used in IS ABM design. The Repast, Recursive Porous Agent Simulation Toolkit, is a widely used free and open-source, cross-platform, agent-based modeling and simulation toolkit. Repast has multiple implementations in several languages, including Java language. Repast is fully object oriented, implemented in Java, C#, and others. We can have variaty of agents and examples from Repast.
- Simulation using different sets of parameters, observe an individual agent's behavior and the behavior as the whole system.
- Analysis the robustnessofthe model using spesific technique.

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