

**Multi-Agent Methodology Project:
Human Immune System Using the GAIA Methodology**

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Human Immune System Simulation

1 Introduction

During our lives an unnoticed war is taking place within our bodies. Everyday our systems are invaded by bacteria, microbes, parasites, viruses and much more. These antigens are unwanted enemies within our bodies and are fought everyday. In this day and age, we are consumed with medical research in areas of Cancer, AIDS, and SARS; which share a common entity: the Human Immune System. Although hands-on research is absolutely necessary, simulations may prove to be extremely useful in that they may save money and time. The immune system itself is made up of many “intelligent” autonomous components, which may lead us to believe that such a system should be built as a multi-agent system.

Throughout this paper we will discuss our design of an Immune System Simulation, mainly with the help of the GAIA methodology.

2 Immune System Introduction

The goal of our project is to design the basic framework of a human immune system. Due to the time restrictions of this course we will select a very specific portion of the human immune system to analyze. Throughout this paper we will present a minimalist view on the adaptive human immune system, more specifically, when a previously encountered antigen has entered the human body. The human immune system is a very complex, intricate, and “intelligent” system that is capable of adapting to ever-changing conditions. Throughout this paper when we mention the immune system we are in fact talking about the human immune system.

We will first discuss how the human immune system works in our minimalist point-of-view and continue from that point on in developing this system. One of the first signs that the human immune system is indeed an intelligent system is that under normal circumstances it will not attack itself. It possesses the ability to determine what actually belongs in the body and what does not by the means of protein markers, that are common to every cell in the body for each individual. Any substance that does not belong in the human body is classified as an antigen. As mentioned earlier, the immune system can distinguish between antigens and normal aspects of the human body by examining proteins. The protein of central interest is known as major histocompatibility complex proteins (MHC), and will be the all important factor in determining antigens. [3]

Before we progress any further, we must state that no one knows exactly how the immune system works, but a very strongly supported theory exists. It is known as the Clonal Selection Theory. This theory states that only specific B and T cells are selected to remove an antigen from the human body. The detection of an antigen within the human body results in only one type of lymphocyte to match up with the antigen and produce the corresponding antibodies to destroy it. [3]

Within the immune system there are two major categories of cells. The first is myeloid progenitor cells and the second category is lymphoid progenitor cells. The myeloid progenitor cells develop into cells that respond early in an immune response. The cells attack antigens in a general manner. In most cases these cells will just engulf and present the antigen to the lymphoid progenitor cells that end up performing the specialized work, to remove the antigen from the human body. We had just mentioned the fact that an antigen would be engulfed by a myeloid progenitor cell, more specifically, a macrophage. For the purposes of our paper, when we discuss the initial immune response, we will only concern ourselves with macrophages. With regards to the lymphoid progenitor cells, we will concentrate on B lymphocytes (B cells), T lymphocytes (T cells), and antibodies. [3]

The B and T cells found within the body can be mapped to at least three levels of differentiation. The three stages are as follows:

1. **Naïve cells** – Cells that exist within the human body, but have not yet encountered an associated antigen.
2. **Effector cells** – Cells that have encountered an associated antigen and are actively involved in eliminating the antigen.
3. **Memory cells** – Cells that remain within the body long after an infection to battle associated antigens at a later time.

These cells are important to the Clonal Selection Theory, but since we are only concerning ourselves with the idea that the immune system has already previously encountered the presented antigen we will be able to ignore some of the stages of cells presented above. In the following paragraphs, we will begin to discuss B cells, T cells, and antibodies in greater detail. [3]

B cells release a soluble substance known as antibodies. These B cells wait around for macrophages to deliver the antigen. If antigen-specific receptors on a B cell match up with the antigen, the B cell will stick to the antigen and will then engulf the antigen. When a Helper T cell arrives, it activates the B cell which results in a transformation of the B cell into a plasma cell that produces specific antibodies to the antigen at an unbelievable rate (10 million copies per hour). The diagram below demonstrates this behaviour: [3]

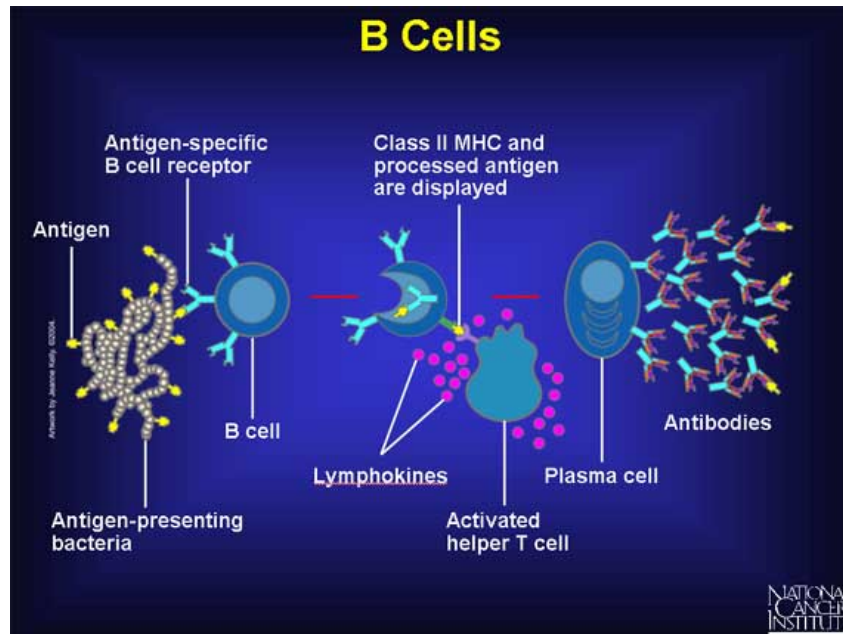


Figure 1: B Cell Diagram

The antibody is in the shape of a Y where its tips vary in shape. It is these specific shapes that allow the antibody to recognize specific antigens. This idea of exactly matching antibodies with antigens is fundamental to the immune system as it is specific antibodies that rid the body of the related antigen. The human body has five types of antibodies. Although there are five types, we will consider them one and the same for our project. The five types are as follows:

1. **IgA** – Represents approximately 15-20% of the body’s antibodies. This antibody helps fight antigens that contact the body’s surface, are digested, or inhaled.
2. **IgD** – Represents approximately 1% of the body’s antibodies. The purpose of this antibody has yet to be determined.
3. **IgE** – Represents an extremely small portion of the body’s antibodies. IgE is actually an antibody subclass and is capable of producing the most powerful immune response.
4. **IgG** – Is very abundant antibody within the human system. It is the only antibody that can pass through the placenta and provide a fetus with its natural protection.
5. **IgM** – Is the most abundant antibody and is mainly responsible for the clumping of red blood cells if the blood received is not compatible with the host’s blood. [3]

T cells on the other hand are absolutely necessary to the immune system. These cells contribute to the immune defense in two ways. They may exist as Helper T cells which help other cells of the immune system or they may exist as specialized T cells called Cytotoxic T cells. Cytotoxic T cells rid the body of antigens themselves by releasing a very powerful chemical that kills the targeted cell on contact. [3] Since this project is under rigorous time constraints, we will only concern ourselves with Helper T cells.

For the sake of our project, we will concern ourselves only with the duration in which the antigen has snuck past our initial defenses (skin, mucus, etc) and is about to be encountered by the cells we have mentioned thus far.

The average human body contains approximately 5 liters of blood. From this there is approximately 4,000 to 11,000 white cells per cubic millimeter of blood according to the Oxford Handbook of Clinical Medicine. One cubic millimeter is equivalent to 1.0×10^{-6} liters. Using simple cross multiplication we can assume that the normal human body possesses in between 20,000,000,000 and 55,000,000,000 immune system cells. In addition to this, approximately 0.1% of these cells match up directly with any specific antigen, meaning that in between 20,000,000 and 55,000,000 cells can directly deal with a specific antigen.

3 System Description

The proposed Adaptive Immune System Simulation (AISS) will be a multi-agent system that is capable of simulating the function of the human immune system, mainly the fundamental cells of the adaptive immune system. As mentioned earlier, we must adhere to a strict time restraint; therefore, our AISS is made up of a few fundamental components. Our AISS will be made up of cells we have already discussed, mainly macrophages, effector B-cells, memory B-cells, antibodies, and helper T-cells.

The AISS will only be able to simulate the absolute basic makeup of the human immune system with a heavy assumption being made.

We are assuming that our simulation will only encounter antigens that have previously been encountered by the immune system. In our introduction to the immune system, we stated that if a B-cell has encountered an antigen already it has the necessary receptors to quickly produce antibodies. For our simulation, we will not worry about the case where the body has not encountered the antigen before. Our application will simulate the course taken by the human immune system given a specific antigen, the Influenza Virus.

4 System Design Documents

In the following section we will use the GAIA methodology to better represent our system. Within the GAIA methodology there are two main stages that we must concern ourselves with: the Analysis and Design stages.

We will begin with the Analysis stage that requires we complete the Roles and Interaction models.

4.1 Roles Model

From examining our system, we can see that we have five roles: **Antigen, Macrophages, Effector B-cells, Helper T-cells, and Antibodies.**

4.1.1 Antigen (Influenza Virus) Role

The first role we will describe is the Influenza Virus as the Antigen. The Influenza virus typically enters the body through the oral or nasal cavity. Some of the cells die, but some of them survive and make their way to the back of the throat. After binding to cells, they then begin to replicate and viral material accumulates in the infected cells. The virus cells then begin to release flu virus particles into the surrounding tissue. This release results in inflammation, which is typically felt as soreness in the throat or even fever. [2]

Note that since the *proteinMarkers* are part of the Antigen, they are not “generated by it”, rather just a property of the Antigen.

Role Schema: ANTIGEN (INFLUENZA VIRUS)	
Description:	Infects respiratory tract and causes "the flu".
Protocols and Activities:	<u>BindToCell</u>, <u>Replicate</u>, <u>ReleaseFluParticles</u>
Permissions:	generates <i>fluVirusParticals // particles that cause inflammation</i>
Responsibilites:	
Liveness:	ANTIGEN (INFLUENZA VIRUS) = (<u>BindToCell</u>. <u>Replicate</u>. <u>ReleaseFluParticles</u>)
Safety:	<ul style="list-style-type: none"> <i>true</i>

Table 1: Antigen Role Schema

4.1.2 Macrophage Role

The second role we will describe is the Macrophage role. The Macrophage role is very simple in nature. It waits until an antigen is encountered, at which point it will engulf the antigen. The Macrophage will produce *chemokins*, which attract other cells of the immune system to the site of infection. While this is occurring, the Macrophage(s) will present a small portion of the antigen for T cells and B cells to examine. As far as the Macrophage role is concerned, this is all that is required. [3]

Note that in our system, we will define the Macrophage's interaction with the T cell only, rather than the T cell and the B cell together.

Role Schema: MACROPHAGE	
Description: Engulfs the antigen and presents a portion of the antigen to other cells of the immune system.	
Protocols and Activities: IdentifyAntigen, EngulfAntigen, AttractCells, PresentAntigen	
Permissions:	
reads	supplied <i>proteinMarkers</i> // <i>proteins contained in antigen</i>
generates	<i>chemokins</i> // <i>substance that will attract other immune cells</i>
generates	<i>surfaceProteinMolecules</i> // <i>presentation of foreign protein to other</i> // <i>cells</i>
Responsibilities:	
Liveness: MACROPHAGE = (IdentifyAntigen. EngulfAntigen. AttractCells. PresentAntigen)^w	
Safety:	
	<ul style="list-style-type: none"> • <i>proteinMarker = foreign</i>

Table 2: Macrophage Role Schema

4.1.3 Effector B Cell Role

The third role of our system is the Effector B cell. The B cell, like the T cell, has receptors that detect specific antigens. When it finds an antigen that matches its receptors it binds to it, and sometimes engulfs it. The B cell then needs to be activated by the T cell. Once this occurs, the B cell can then divide and produce *plasma cells* and *memory cells*. The plasma cells are responsible for producing antibodies, and the memory cells help achieve immunity from its particular antigen as it can recognize the intruders, and begin eliminating them much faster. [1]

Since the Gaia methodology does not allow for the dynamic creation of roles, we will not be representing the production of memory cells and plasma cells from the B cell.

We may refer to the Effector B Cell as “B cell” for the sake of simplicity.

Role Schema: EFFECTOR B CELL
Description: Binds to antigen, and if necessary, combats it.
Protocols and Activities: BindToAntigen, AwaitActivation, <u>Divide</u>
Permissions: reads <i>supplied proteinMarkers // proteins contained in substances</i>
Responsibilities: Liveness: EFFECTOR B CELL = (BindToAntigen. AwaitActivation. <u>Divide</u>)^w
Safety: • <i>proteinMarker = identified</i>

Table 3: Effector B Cell Role Schema

4.1.4 Helper T Cell Role

The Helper T Cell is the fourth role in our system, and plays a major role in immune defense. The Helper T Cell first identifies an antigen using its receptors (in the same way the B cell does). Once it locates an antigen that it recognizes, the Helper T Cell must initiate the battle against the intruders, or they will prevail. [1] This requires the Helper T Cell to divide, and activate the B cell, by releasing extracellular signals called *cytokines*, so that the B Cell knows it can begin producing antibodies to fight the antigens. [4]

We may refer to the Helper T Cell as “T cell” for the sake of simplicity.

Role Schema: HELPER T CELL
Description: Activate and direct other immune cells.
Protocols and Activities: IdentifyAntigen, ActivateBCell, <u>Divide</u>
Permissions: reads <i>supplied proteinMarkers // proteins contained in substances</i> generates <i>cytokines // activate B cells</i>
Responsibilities: Liveness: HELPER T CELL = (IdentifyAntigen. ActivateBCell. <u>Divide</u>)^w
Safety: • <i>proteinMarker = identified</i>

Table 4: Helper T Cell Role Schema

4.1.5 Antibody Role

The final role in our immune system is the Antibody. Antibodies directly combat antigens by binding to their surface causing them to clump together, which slows they're spread throughout the body. They also block antigen receptors which prevents the antigen from attaching to any new cells. Their binding also assists other immune cells to efficiently process the viral particles. [2]

Role Schema: ANTIBODY
Description: Combats foreign substances in body.
Protocols and Activities: BindToAntigen, BlockReceptors
Permissions: reads supplied <i>proteinMarkers</i> // proteins contained in substances
Responsibilities: Liveness: ANTIBODY = (BindToVirus. BlockReceptors)
Safety: • <i>proteinMarkers = identified</i>

Table 5: Antibody Role Schema

4.2 Interaction Model

In the Interaction model, we will depict the interactions between all the roles, including the information exchanged or created within those interactions.

4.2.1 Macrophage Interaction Model

IdentifyAntigen		
Macrophage	Antigen	supplied proteinMarkers
Identify foreign proteins on antigen		

Table 6: IdentifyAntigen Interaction

EngulfAntigen		
Macrophage	Antigen	
Engulf antigen		

Table 7: EngulfAntigen Interaction

AttractsCells		
Macrophage	T Cell B Cell	
Release chemokins to attract immune cells		chemokins

Table 8: AttractCells Interaction

PresentAntigen		
Macrophage	T Cell	
Presntation of foreign proteins for T Cell to read		surfaceProteinMolecules

Table 9: PresentAntigen Interaction

4.2.2 B Cell Interaction Model

BindToAntigen		
B Cell	Antigen	supplied proteinMarkers
Binds to antigen		

Table 10: BindToAntigen Interaction

AwaitActivation		
B Cell	T Cell	
Wait for T Cell to activate B Cell		cytokines

Table 11: AwaitActivation Interaction

4.2.3 T cell Interaction Model

IdentifyAntigen		
T Cell	Antigen	supplied proteinMarkers
Identify foreign proteins on antigen		

Table 12: IdentifyAntigen Interaction

ActivateBCell		
T Cell	B Cell	cytokines
Activates B Cell to combat Antigen		

Table 13: ActivateBCell Interaction

4.2.4 Antibody Interaction Model

BindToAntigen		
Antibody	Antigen	supplied proteinMarkers
Binds To Antigen		

Table 14: BindToAntigen Interaction

BlockReceptors		
Antibody	Antigen	
Block Antigen Receptors		

Table 15: BlockReceptors Interaction

The next portion of the GAIA methodology is the Design Model. The Design model consists of the Agent model, Service model and Acquaintance model.

4.3 Agent Model

The Agent model will exhibit all the Agent types involved in the system, as well as the roles associated with them.

In order to determine what our Agent model should look like, it is necessary to consider each of our roles and their interdependence with all other roles. From this analysis we can determine if one role is closely coupled to another, and should hence be included in the same agent type.

First we will consider the Antigen. It is clear that the Antigen role is very independent of all the other roles, as its purpose is to attack, whilst the rest are to defend.

Next we consider the Macrophage. Although the Macrophage's general purpose is similar to the B cell, T cell, and the Antibody, it's main function is to supply information to other cells. It has no significant dependencies on any other role in the system.

The next role to consider is the Effector B cell. This role is responsible for producing cells to attack the invading antigen and rid the Influenza Virus (in our model). However, the B cell cannot act before being activated by the Helper T cell. For this dependency, we believe that the B cell and T cell should belong to the same agent type.

Finally, like the Antigen and the Macrophage, the Antibody acts independently of the other roles and therefore will be contained in its own agent type.

With regards to the number of agents existing in the system, we were unable to find accurate number for every agent except the WhiteCellAgents. However, once determined, all the values will be scaled down proportionately so that there are a reasonable number of agents in our system.

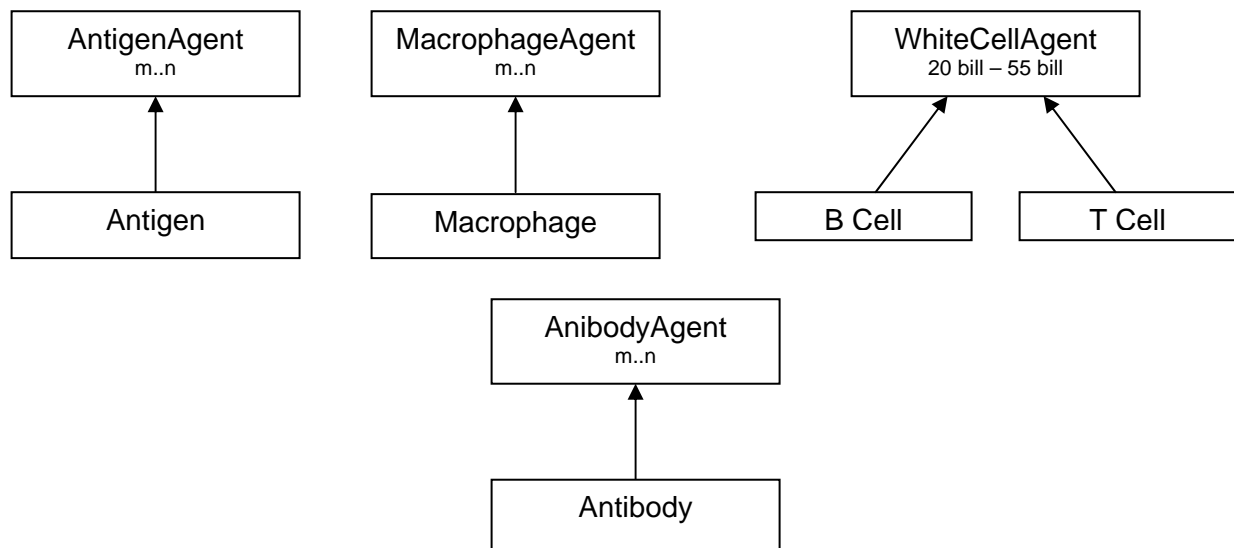


Figure 2: Agent Model

4.4 Service Model

The Service model will describe the services available from each Agent. They are slightly more descriptive than the other models completed thus far, as they describe the inputs, outputs, pre-conditions, and post-conditions of each service.

Table 16: Antigen Agent Service Model

Service	Inputs	Outputs	Pre-Condition	Post-Condition
Bind to Cell			true	true
Replicate			true	true
Attack		<i>flu particles</i>	true	true

Table 17: Macrophage Agent Service Model

Service	Inputs	Outputs	Pre-Condition	Post-Condition
Identify Antigen	<i>proteinMarkers</i>			<i>proteinMarkers = foreign</i>
Engulf Antigen			<i>proteinMarkers = foreign</i>	true
Signal Immune Cells		<i>chemokins</i>	true	true
Present Antigen Information		<i>proteinMarkers</i>	true	true

Table 18: White Cell Agent Service Model

Service	Inputs	Outputs	Pre-Condition	Post-Condition
Bind to Antigen	<i>proteinMarkers</i>		true	<i>proteinMarkers = identified</i>
Await Activation From T Cell			<i>proteinMarkers = identified</i>	true
Divide			true	true
Identify Antigen	<i>proteinMarkers</i>		true	<i>proteinMarkers = identified</i>
Activate B Cells		<i>cytokines</i>	<i>proteinMarkers = identified</i>	true
Divide			true	true

Table 19: Antibody Agent

Service	Inputs	Outputs	Pre-Condition	Post-Condition
Bind to Antigen	<i>proteinMarkers</i>		true	<i>proteinMarkers = identified</i>
Block Receptors			<i>proteinMarkers = identified</i>	true

4.5 Acquaintance model

The Acquaintance model displays the lines of communication between agents. Although there are interactions among agents, these do not necessarily constitute paths of communication between agents. In our system, there are few interactions that we consider to occur via communication links. These are the Macrophage signaling the T cell that it has encountered an antigen, and the activation of the B cell from the T cell. Since the T cell and the B cell are included in the WhiteCellAgent, their interaction will not be represented in this model. That only leave the interaction between the Macrophage Agent and the T cell which is contained in the WhiteCellAgent.

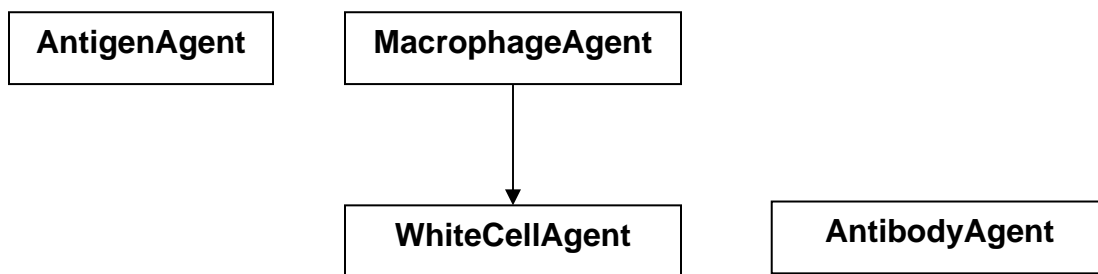


Figure 3: Acquaintance Model

5 System Description

The following sections will describe the system in more detail with regards to specific functionality and architecture.

5.1 System Description Diagram

The System diagram below show the elements involved in using the AISS Application. The user will select an Influenza virus to enter into the system via the GUI, which provides the backend of the Application with the information specified by the user. The Application will then interact with the database in order to perform the necessary simulation.

The Influenza Virus Database will contain information about different influenza viruses, including their approximate load when entered into the human system. This load will take into consideration the cells that die off, or that do not bind to other cells. What this means is that the number of virus cells specified by the database will be assumed to bind to cells within the human system, and be active within the system.

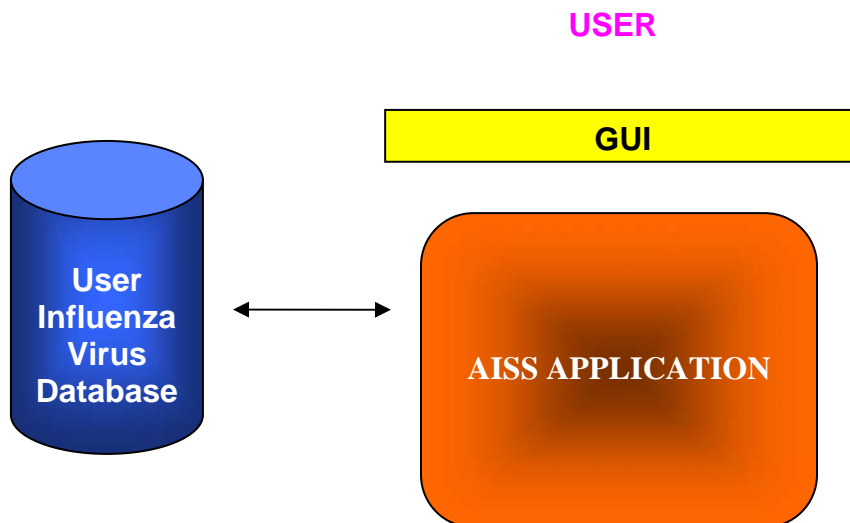


Figure 4: System Design Components

5.2 Communication Protocol: Interfaces

The agents in our system will communicate with each other using Interface methods. This is a simple and effective method of communication for a stand-alone application. The main reason for using Interfaces as the means of communication is for future expansion of the system. Currently the system is simple enough that conventional class method calls would suffice. However, if in the future our system was to be expanded to include variations of the current immune system agents, or even remote immune system agents (which may or may not require the use of services), Interfaces would allow for the overall increase in complexity of the system to occur very easily.

The Class Diagram, (figure 9), displayed in section **5.3.2** describes the basic interface structure to be used in our system.

5.3 Detailed Design

5.3.1 Use Cases

This section will describe use cases and use case definitions for all the participating agents.

That includes:

- Antigen Agent
- Macrophage Agent
- WhiteCell Agent
- Antibody Agent

5.3.1.1 Antigen Agent

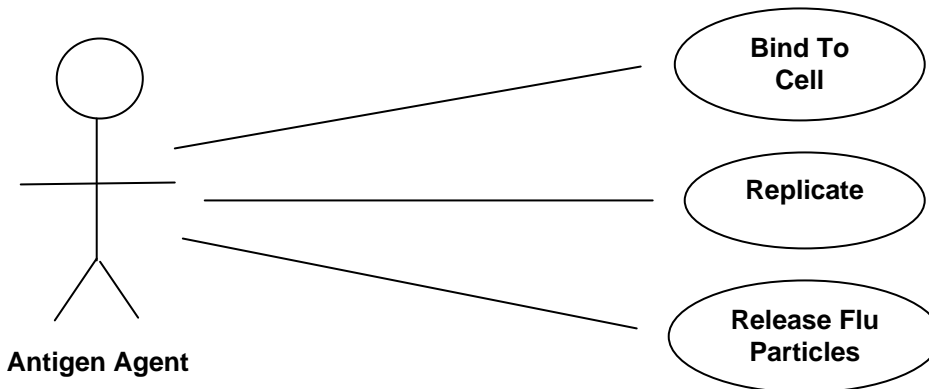


Figure 5: Antigen Agent Use Case Diagram

5.3.1.1.1 Use Case: *Bind To Cell*

Actors: Antigen Agent
Pre-Conditions: none
Post-Conditions: none
Basic Flow: 1. Find cell
2. Bind to cell
Alternate Flows: none
Relationships: none

5.3.1.1.2 Use Case: *Replicate*

Actors: Antigen Agent
Pre-Conditions: none
Post-Conditions: none
Basic Flow: 1. Replicate
Alternate Flow: none
Relationships: none

5.3.1.1.3 Use Case: *Release Flu Particles*

Actors: Antigen Agent
Pre-Conditions: none
Post-Conditions: none
Basic Flow: 1. Release Flu Particles
Alternate Flow: none
Relationships: none

5.3.1.2 Macrophage Agent

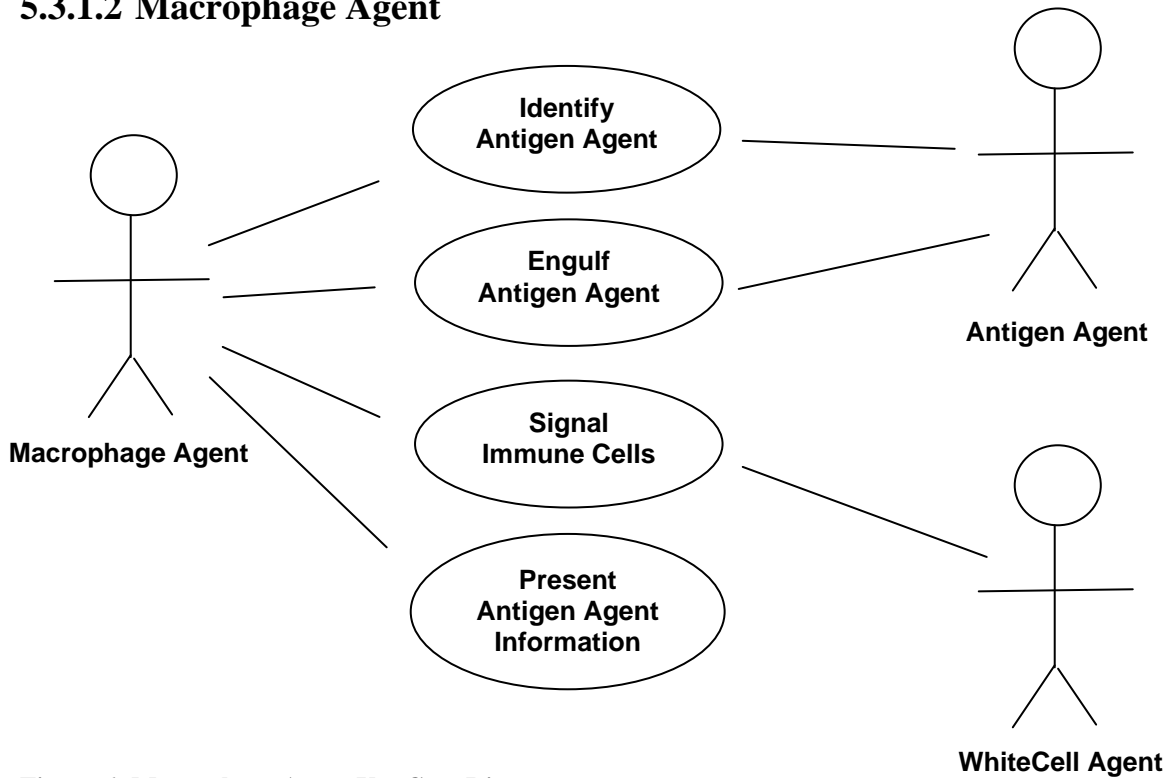


Figure 6: Macrophage Agent Use Case Diagram

5.3.1.2.1 Use Case: *Identify Antigen*

Actors: Macrophage Agent, Antigen Agent
 Pre-Conditions: none
 Post-Conditions: protein markers = foreign
 Basic Flow:
 1. Retrieve protein make up of Antigen Agent
 2. Verify that it is foreign
 Alternate Flows: none.
 Relationships: none.

5.3.1.2.2 Use Case: *Engulf Antigen*

Actors: Macrophage Agent, Antigen Agent
 Pre-Conditions: protein markers = foreign
 Post-Conditions: none
 Basic Flow:
 1. Engulf Antigen Agent
 Alternate Flows: none.
 Relationships: none.

5.3.1.2.3 Use Case: Signal Immune Cells

Actors: Macrophage Agent, WhiteCell Agent
Pre-Conditions: none
Post-Conditions: none
Basic Flow: 1. Release chemokins to attract WhiteCell Agent
Alternate Flows: none.
Relationships: none.

5.3.1.2.4 Use Case: Present Antigen Information

Actors: Macrophage Agent
Pre-Conditions: none
Post-Conditions: none
Basic Flow: 1. Surface antigen information
Alternate Flows: none.
Relationships: none.

5.3.1.3 WhiteCell Agent

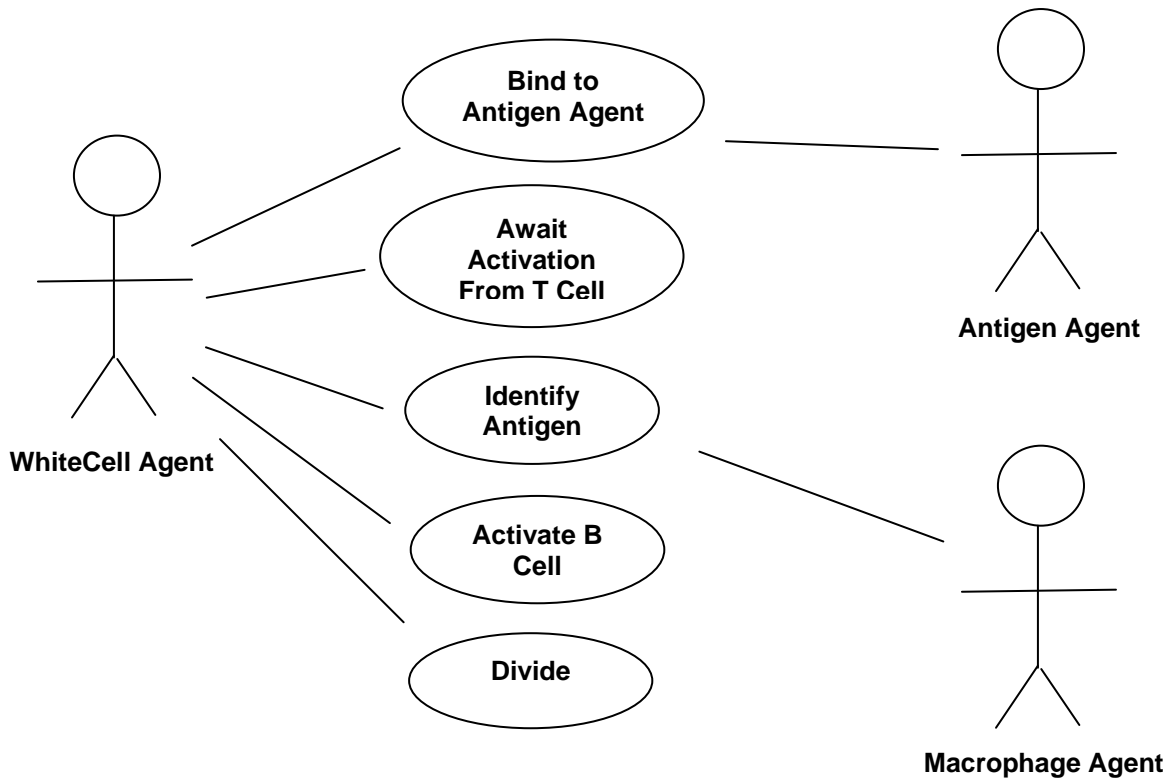


Figure 7: WhiteCell Agent Use Case Diagram

5.3.1.3.1 Use Case: Bind to Antigen

Actors: WhiteCell Agent, Antigen Agent
Pre-Conditions: none
Post-Conditions: protein markers = identified
Basic Flow: 1. Match B Cell receptors to Antigen Agent protein markers
2. Bind to Antigen Agent
Alternate Flows: none.
Relationships: none

5.3.1.3.2 Use Case: Await Activation From T Cell

Actors: WhiteCell Agent
Pre-Conditions: protein markers = identified
Post-Conditions: none
Basic Flow: 1. Await activation from T Cell
Alternate Flows: none.
Relationships: none

5.3.1.3.3 Use Case: Identify Antigen

Actors: WhiteCell Agent, Macrophage Agent
Pre-Conditions: none
Post-Conditions: protein markers = identified
Basic Flow: 1. Match T Cell receptors to Macrophage Agent's surface information
Alternate Flows: none.
Relationships: none

5.3.1.3.4 Use Case: Activate B Cell

Actors: WhiteCell Agent
Pre-Conditions: protein markers = identified
Post-Conditions: none
Basic Flow: 1. Release cytokines to activate B Cell
Alternate Flows: none.
Relationships: none

5.3.1.3.5 Use Case: Divide

Actors: WhiteCell Agent
Pre-Conditions: none
Post-Conditions: none
Basic Flow: 1. Trigger dividing of T Cell
2. Trigger dividing of B Cell
Alternate Flows: none.
Relationships: none

5.3.1.4 Antibody Agent

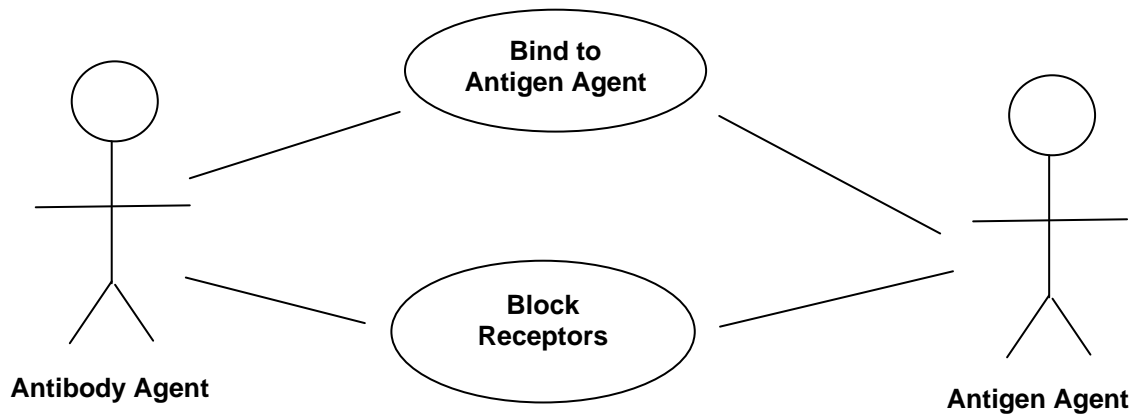


Figure 8: Antibody Agent Use Case Diagram

5.3.1.4.1 Use Case: *Bind to Antigen Agent*

Actors: Antibody Agent, Antigen Agent
Pre-Conditions: none
Post-Conditions: protein markers = identified
Basic Flow:
1. Match Antibody Agent receptors to Antigen Agent protein markers
2. Bind to Antigen Agent
Alternate Flows: none.
Relationships: none

5.3.1.4.2 Use Case: *Block Receptors*

Actors: Antibody Agent, Antigen Agent
Pre-Conditions: protein markers = identified
Post-Conditions: none
Basic Flow:
1. Block receptors of Antigen Agent
Alternate Flows: none.
Relationships: none

5.3.2 Class Diagram

The Class Diagram will illustrate how each class in our system is related to other classes, as well as the methods and interfaces used for each class. All the immune system classes (Macrophage, EffectorBCell, HelperTCell and Antibody) inherit from the ImmuneSystemCell class. Since immune cells have a lot of functionality in common, as they may be added to our system, their common methods can be added to this parent class. This principle goes for each of the interfaces as well.

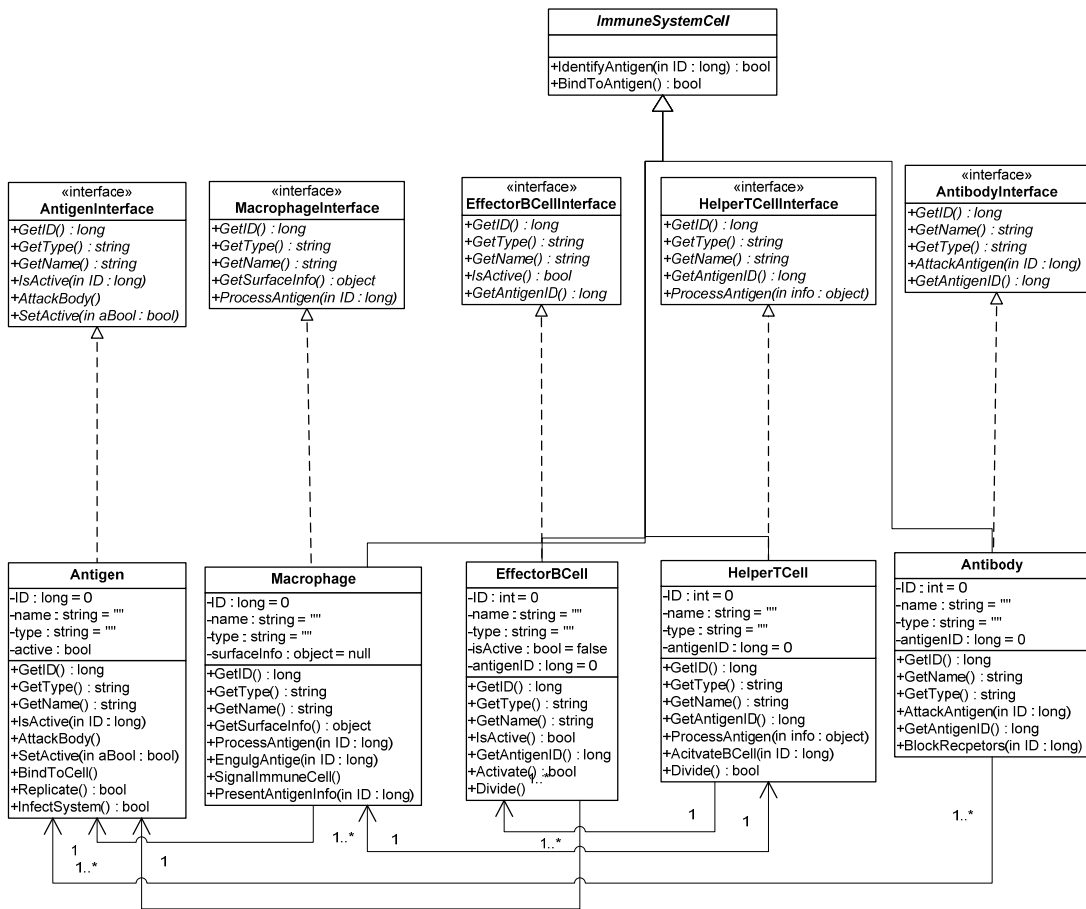


Figure 9: Class Diagram

5.3.3 Sequence Diagram

The Sequence Diagram will show how the classes interact with each other, and will also convey the sequence of interactions between them.

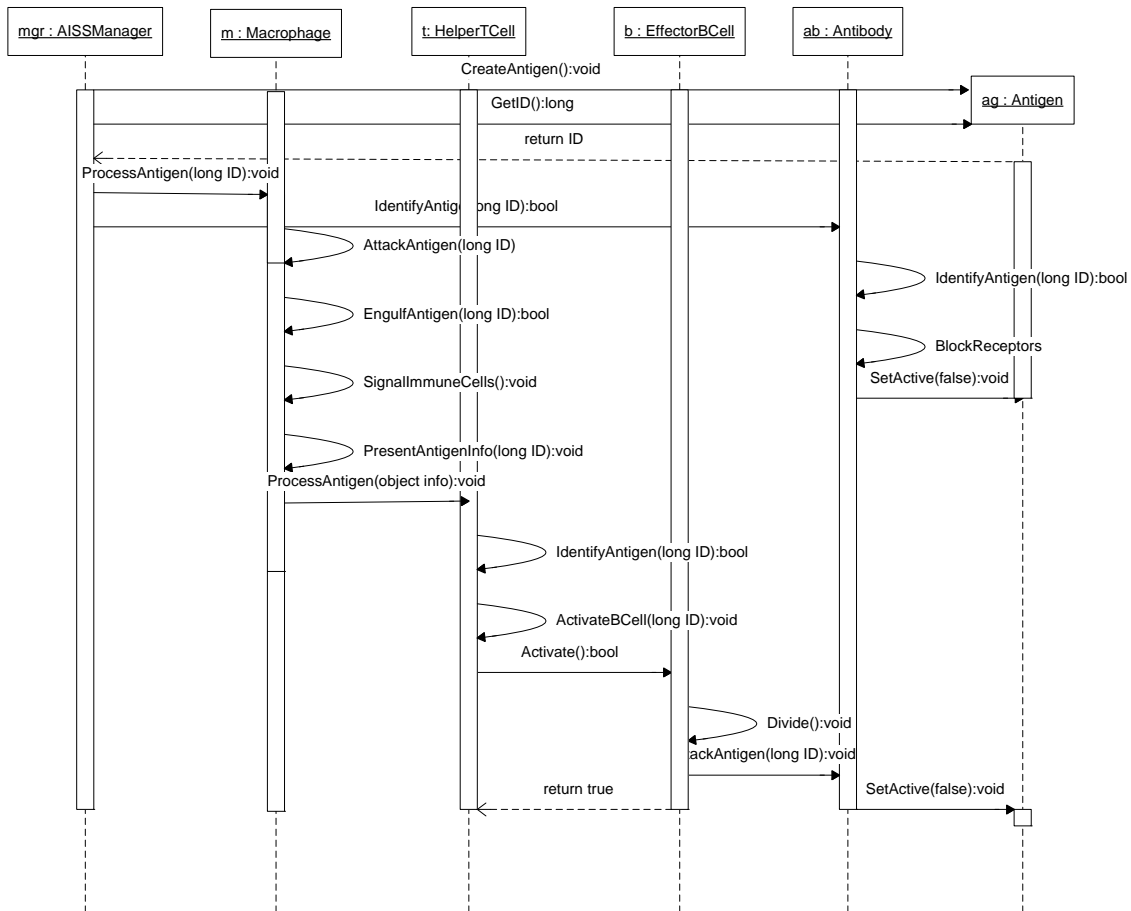


Figure 10: Sequence Diagram

6 References

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