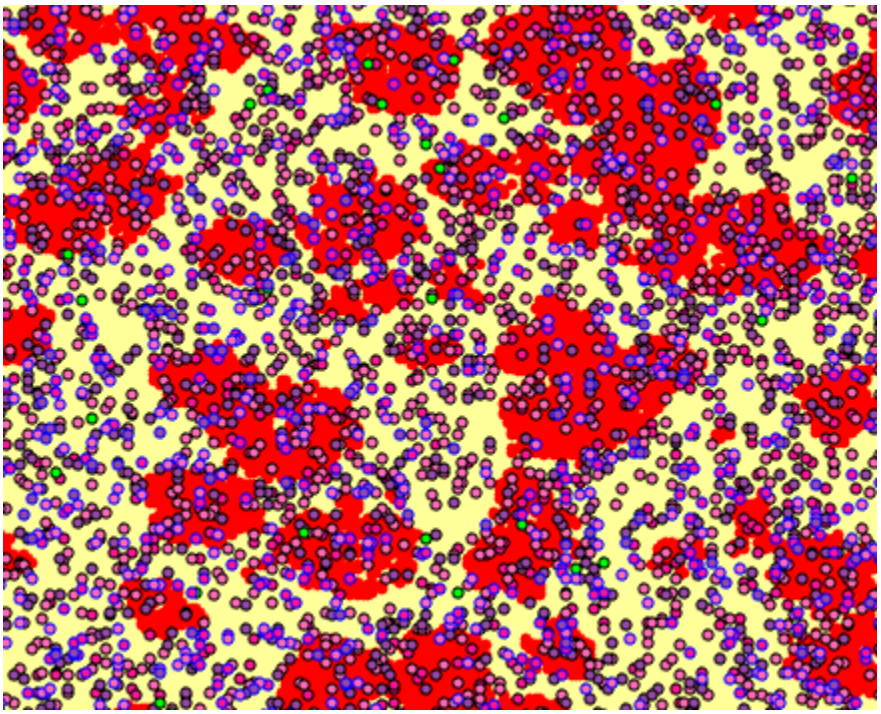

Energy Estimations And The Creation Of An Artificial Immune System

Master's thesis in physics

Lars Liberg Department Of Physics
Chalmers University Of Technology
Gothenburg, Sweden 2019

Master's Thesis 2019

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Abstract

The dawn of the information era is upon us and yet there are many unresolved mysteries in the universe, one among them are the governing mechanism behind our own immunity. By keep researching with relevant questions we might someday find the answer to that simple question.

In order to investigate this question further one must first learn the basics of immunology and from there try to advance towards the goal. Obviously this question could not be answered, mostly due to lack in knowledge concerning energy expenditure in immune cell activation and alike. Instead energy expenditures by different systems/organs of our body are investigated and compared to our recommended calorie intake, in order to see how well the numbers add up. This comparison is important because the energy we eat should be equal to the energy we spend daily (if we maintain the same weight), because today, food is the only source of energy we know about.

The second part of this master's Thesis concerns agent based models to simulate an adaptive immune response. The results from the simulations are quite obvious but the important thing is that the code capture some dynamics which the real immune system shows. Usually one does not simulate an immune response because it is too large to consider.

Keywords: Immune system, energy, lymphocytes, killer cells, immunity, health, T-cells, B-cells, macrophage, adaptive immunity, agent based model, energy expenditure, infection, pathogen, phagocyte.

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Contents

Chapter 1

Introduction

The field of immunology may be the most complex and unexplored field in modern science. Yet ever since the becoming of our species, people of all times have stopped and thought "why am I alive?", "why am I sick and not them?", "why does some survive and some people not?", all of these questions sooner or later comes down to the immune system in the field of immunology (if not one is killed instantly by a wild animal, genetic disorder, accident or murder). Still modern science are far from an answer to how our immune system work, after centuries of research and thinking.

Modern science have categorized a large amount of cells and molecules cooperating in order to protect the body, which is several thousands, but we have no clue what mechanism(s) the body may alter naturally in order to improve the system as a whole. Is it that hard to identify and measure?

1.1 Report Structure

The report starts with some background and history in immunology in order to get acquainted with the subject. Then the immune system is described in more detail in chapter 2 which will enable the reader to understand difficulties to measure energies and other properties of the immune system, and receive insight enough to understand the most important functions of the immune system. Chapter 3 goes through energy estimations of different organs or systems in our body and how much energy we should consume per day. Chapter 4 explains the code I have written which simulates an adaptive immune response, it is highly recommended to read chapter 2 before this chapter. Chapter 5 presents results made from energy estimations in chapter 3 and simulations from the code described in chapter 4. The last chapters are discussion, conclusion and future work yielded from interpreting the results. In appendix A you can view the code described in chapter 4.

1.2 Background

The immune system holds many mechanisms yet to be understood due to its complexity. The immune system have several thousands different molecules and cells working together as a whole to maintain life for the organism. If these mechanisms are to be revealed the field of immunology will make tremendous progress and we reveal more secrets of how nature and life works.

All life in the universe must have an immune system, or else life can't exist. Plants for example have an immune system which is integrated with the soil beneath it, in return for the nutrition the soil brings to the plant, it returns other compounds vital for the ecosystem in the rhizosphere microbiome (the soil closest to the roots of the plant). If infectious agents ruins the microbiome in the rhizosphere the plant will become sick and die, so the immune system extends outside the plant. [5]

In cultures of bacteria the immune system consists of communication substances between the individual bacteria in a process called quorum sensing. These communication substances then synchronise the population and make them work as a group in order to increase their survival rate. By quorum sensing bacteria are able to create a biofilm protecting the population and make the population to behave like a multicellular organism [6].

The immune system in higher mammals and humans are much more complex and consist of many different systems and mechanisms. For starters we have an innate immune system which is the first line of defence against foreign invaders. The most important cells fighting invaders in the innate immune system are macrophages and neutrophils, they are present in the bloodstream which enables them to protect the whole body. Around 1% of the blood consists of white blood cells in which macrophages and neutrophils are included [7][8]. Higher mammals such as humans also have an adaptive immune system, complementing the more primitive innate immune system. The adaptive immune system is able to attack specific viruses, bacteria, infectious agents, fungi or parasites which the innate immune system can't fight off, the adaptive immune system is triggered when antigens are detected by immune cells, after finding a suitable candidate for fighting the infectious agent (by finding a match for the antigen) a tremendous amount of antibodies that match the antigen are released and production of T-cells, T helper-cells and B-cells with the correct antigen receptors are manufactured in large quantities [9].The adaptive immune system cells, namely T-cells, Th-cells and B-cells move mainly trough the lymphatic system which is a large network reachig all parts of the body, then when the T-cells have reached the infected region they exit the lymphatic system through a lymph node located near the infected area into the bloodstream [10].

1.3 A brief history of immunology

The notion of immunity have been around for thousands of years, starting with believing that diseases where caused by evil deeds or thoughts haunting ones soul and causing the physical body to suffer.[1] The ancient sects which is the precursors of modern Buddhism coins the concept of karma around 400 B.C, if one have good karma no illness will come. [2]

The very first clinical description of immunity dates back to the 9th century, the study is called 'A Treatise on Smallpox and Measles' and is written by the islamic physician Al-Razi. [1].

It's not until 1796 Edward Jenner discover that if an animal is subjected to small amounts of cowpox it will induce the protection of the deadly disease smallpox. The method was named vaccination, the important discoveries made where that the body learns to recognize the disease and thus better protected against it, and that microorganisms is causing the disease and not some supernatural force, therefor the scientific approach in immunology could be set into motion.

In the 1890s Emil von Behring and Shibasaburo Kitasato discovered the reason why vaccination enhanced protection against future diseases of the same kind. This is due to agents that appear in the body of the vaccinated, they came to call these agents antibodies. They later received the Nobel prize in 1901 for their discovery of antibodies.

In 1982 Elie Metchnikoff showed that invertebrates and mammals have cells that "eat" invading microorganisms, the cells where named phagocytes (phag meaning "a thing that devours"[68], cyte is the final element in a compound word [69]). After Metchnikoff made this discovery he suggested that antibodies where of little importance which of course lead to a dispute. In 1904 the conflict was resolved by Almroth Wright and Joseph Denys which demonstrated that the antibodies binds to bacteria and promotes the phagocytes to attack the invading microorganisms.

Paul Ehrlich formulated a theory named side chain theory in the 1890s, which essentially states that white blood cells are covered with several side chains and he also invented a method to estimate the amount of antibodies in the blood. He also showed that when the receptors on the surface of B-cells binds to an antigen it triggers what we later would call an immune response, which produces large amounts of antibodies capable of eliminating the foreign invader. In order to produce the required antibodies given an antigen another theory where proposed by Ehrlich called the providential (or germinal) theory. The providential theory suggests that if an antigen binds with a B-cell receptor then that cell is responsible for both selecting and stimulating the desired B-cell for fighting the infection. In the year 1908 both Metchnikoff and Ehrlich received the Nobel prize for their works on the immune system.

Between 1910 and 1930 experiments made by Jules Brodet and others led to

the abandonment of Ehrlich's theory regarding selection of the B-cells for more than a half century, Jules Brodet also received a Nobel prize in 1919 for the discovery of proteins working together in eliminating extracellular pathogens called the complement system.

Finally in the 1950s Niels K. Jerne revived Ehrlich selective theory of antibody formation. He assumed that a diverse population of antibodies where present in the blood stream even though no antigen where present. But it was Burnet who formalized a lasting theory for the process. It goes "The selective event is the stimulus given by the antigen, where those cells produce antibodies complementary to it will proliferate (clonal expansion) and secrete antibodies". It was formulated 1959 and called clonal selection theory. Peter Medawar later confirmed this experimentally and they both received the Nobel prize for their efforts.

Later in the early 1980s Susumo Tonegava published his studies concerning structure and diversity of the antibody molecules. He proposed that from reproductive cells contain multiple genes scattered along a chromosome contains information to code antibody molecules. He received the Nobel prize in immunology for this in 1987 [3].

The Nobel prize in 2018 went to James P. Allison and Tasuko Honjo for their discovery of a cancer treatment that inhibit the breaking mechanisms in the immune system which make the immune system itself fight the tumor instead of a poison or outside agent attacking the tumor [4].

1.4 Purpose

Primarily my purpose was to find a mechanism that governs the immune system as a whole, i.e. determines if the immune system is "good" or "bad". But it was impossible to answer on the time frame for the master's thesis. Therefor the purpose changed into the following paragraph.

The first part of this work is to map the energy consumption in different organs and systems in the human body, in order to verify that existing data is consistent with our recommended calorie intake. The second part of this work is to simulate an adaptive immune response using agent based modelling, in order to emulate an immune response and see if any remarkable dynamics arises.

1.5 Method

The data of energy consumption's in different organs and systems in the body will be collected by reading existing data in articles, books, reports and websites, then the data will be studied in order to make relevant results and conclusions.

The program for the simulation of an adaptive immune response will be written in MATLAB by an agent based modelling view. Then run several simulations in order to find relevant dynamics and draw conclusions about the validity of the simulation in its purpose of emulating the real immune system.

Chapter 2

Theory

The immune system is a complex adaptive system consisting of thousands of chemical reactions and molecules. In order to understand the sum of all the parts the best thing is to look at it in a holistic perspective first and then go down to the details, therefor this section begins with an overview with much grater detail than in the background section. After that more specific parts and functions of the immune system is described.

After that section 2.4 goes through the basics in metabolism, basal metabolic rate and some other aspects regarding our digestion and food consumption.

2.1 An overview of the human immune system

The immune cells responsible for the defense against foreign invaders are called white blood cells and constitutes 1 % [8] of the blood. White blood cells are divided into three groups, lymphocytes, granulocytes and monocytes, all of them have different functions and purpose for the defence against foreign invaders [11].

Lymphocytes are the immune cells that belongs the the adaptive immune system, except for the natural killer cells (NK-cells) which belongs to the innate immune system [12]. The lymphocytes circulate through the body by the lymphatic system entering the bloodstream via lymph nodes distributed all over the body, see figure 2.1. They specialize to exterminate specific foreign invaders.[10, 11] For example if the body gets exposed to disease X, then the adaptive immune system learn to fight this disease and remember how to fight it, so next time the body gets exposed to disease X the immune system is prepared and eliminates the disease before any major damage has occurred.

Granulocytes are responsible for fighting large infectious agents and they are also important for different infections. The most common granulocyte is the neutrophil constituting 50-80 % of all white blood cell cells. There are also eosinophils

and basophils. Together these three granulocytes act on different signals, signals from damaged tissue, proteins in the blood plasma or signaling substances directly secreted from invading microorganisms. Granulocytes have a lifespan of a few days and are regularly produced by cells in the bone marrow, and are always present in the bloodstream. They eliminate invaders by digesting them in a process called phagocytosis. [11, 13, 14]

Monocytes make up 4-8 % of the white blood cells present in the bloodstream. The monocytes are relatively large immune cells that travels to places that are infected in the body, when they arrive they differentiate into macrophages. Macrophages like neutrophils phagocytose whole infectious agents, but they also clean up dead microorganisms which makes them very important on areas of infection since a lot of cells die there. [11]

The innate immune system cells are made up by different monocytes and granulocytes while the adaptive immune cells are constituted by lympocytes. The Granulocytes and monocytes have the same functions throughout life whilst the lymphocytes learn and adapt over time. The innate immune system might be able to kill the same invaders as the adaptive immune system but when an infection is to great for the innate defence, the adaptive immune system is activated and it produces an army of cells eliminating the infectious agents [15].

2.2 The innate immune system

The white blood cells in the innate immune system is the granulocytes, monocytes and the natural killer cells. The granulocytes consist of three white blood cells, namely basophils, eosinophils and neutrophils. The important immune cell of the monocytes are the macrophages. The natural killer cell is unlike the other immune cells in the innate immune system a member of the lymphocytes which in general belongs to the adaptive immune system. Mast cells and dendritic cells also have significant roles to play in the innate immune system. On top of all this there exist a complementary immune system which is classified as a part of the innate immune system, the complementary immune systems main purpose is aid and improve the functioning of the immune cells both in the adaptive and innate immune system.

2.2.1 Surface barriers

The very first inherited line of defence is surface barriers such as skin, cellular membranes and other protective tissues separating our body from the outside world full of all kinds of dangerous microorganisms. First pathogens encounter our skin, if they succeed to enter our body the individual cells are protected by cell membranes. Our body can't be completely isolated from the outside world,

we need to breathe, eat and get rid of superfluous components in the body. As an example our lungs have specialized a tissue letting through least possible molecules, the gastronomical tract extracts important nutrition and keep the useful bacterial culture intact, while keeping harmful compounds, bacteria and others away from the internal body. Obviously some invaders succeeds to enter the human body and that is when the white blood cells takes over [16].

2.2.2 Granulocytes

Neutrophils

The neutrophils make up 50-80 % of all white blood cells and they are basically round in shape with a diameter from 9-15 μm. The direction in which they move mainly depends on the concentration of a signaling substance secreted in areas of damaged tissue, i.e the tissue is damaged because pathogens (collection name for harm-full foreign invaders) are present and injure the cells in that area. They eliminate the pathogens by eating them whole by a process called phagocytosis. A normal adult person produces 100 billion neutrophils on a daily basis from stem cells in the bone marrow, it takes about a week for a neutrophil to mature from the stem cell stage [14, 17].

Eosinophils

Eosinophils constitutes 1-3 % of all white blood cells in the blood stream. Beyond the blood stream they reside in several places in the body, in the medulla, junction between cortex and medulla, the lower gastrointestinal tract, medulla of the thymus, lymph nodes, ovary, uterus and spleen. Eosinophils are 12-17 μm in diameter, have a half life from 6-12 hours while circulating, this time is extended to 8-12 days if they reside in tissue. Their main function in the immune system is to eliminate parasites since they contain a protein which is toxic to most parasites. They also kill unwanted microorganisms like the neutrophil and have a key role in immediate hypersensitive reactions, for example people who are allergic to peanuts might die if they come in contact with them [18, 19].

Basophils

After the discovery of the basophil a half century ago it is still uncertain what functions the basophil is carrying out in the body. The most investigated function is the distribution of histamine, seretonin and leukotrienes throughout the body which is stored in cell tissue. These compounds causes to contraction of smooth muscule tissue of the lungs, tension in the stomach and lower blood pressure. Histamine also signals nerve cells and they are very important for the natural

inflammatory response, which is essential during an inflammation, without the inflammatory response the immune cells would not know where to fight the intruders. The basophils constitutes less than 1% of the blood in the bloodstream [20, 21, 22].

2.2.3 Monocytes

Monocytes make up 3-8 % [26] of the white blood cells in the blood stream. The actual monocyte does not eliminate any infectious agents, instead it travels through the blood stream and by secreted signaling substances monocytes starts to differentiate into macrophages. The macrophages have a simular function as the neutrophils when digesting foreign microbes, but they also digest dead cells and tissue in the local surroundings. Unlike all other immune cells the macrophages are stationary and is rather classified as a tissue than a blood cell, macrophages usually settles nearby lymphocyte tissue (e.g spleen, lymph nodes..), this might depend on their antigen presenting function which triggers the adaptive immune system, hence lymphocytes are nearby and can therefore register the antigen that the macrophage presents and initiate a specialized attack.

The research concerning macrophages are far from complete, but for now it is relatively certain that their most important functions are elimination of pathogens, digestion of damaged cells and working as an antigen presenting cell in order to trigger the adaptive immune response [27, 28].

It is also worth mentioning that monocytes also differentiate to (myeloid) dendric cells whose primary task is to act as antigen presenting cells in order to activate the adaptive immune system [29].

2.2.4 Natural killer cells

Natural killer cells (NK cells) make up 7 % [23] of the lymphocytes in the bloodstream (and lymphocytes make up 20-30% of the white blood cells in the bloodstream [24]). In contrast to most immune cells of the innate immune system natural killer cells are programmed to kill the malfunctioning cells of our own body, e.g. virus infected cells or cancer tumors. Natural killer cells detect these malfunctions from signal substances secreted by the cells, when the abnormal cells are detected it inserts a "poison" into the cell that causes the cell to burst and die. Natural killer cells also secrete cytokines which promotes other immune cells. All functions of the natural killer cells are not completely understood but they play a very important role in the immune system [25, 27].

2.2.5 Mast cells

Mast cells are a tissue associated with the innate immune system. Its main functions are histamine (signaling substance to other cells and systems) secretion which causes smooth muscles to contract and works as a neurotransmitter between nerve cells [22]. The mast cells are mainly located adjacent to skin, blood vessels, nerves, "breathing system" and in the tract. Mast cells also play an important role in inflammation and swelling, which makes it possible for the immune cells to find the parts of the body that is under siege [32].

2.2.6 The complement system

In addition to the white blood cells the innate immune system have more than 30 proteins [31]circulating in the bloodstream that works together in order to enhance the efficiency of the white blood cells and kill pathogens. The collaboration of these proteins working for the innate immune system is called the complement system. It has three main functions, opsonization, membrane attack complex and protein activation cascade.

Opsonization is when proteins of the complement system attaches to the surface of a pathogen which makes it easier for the white blood cells to identify the invading pathogens.

Membrane attack complexes is loosely speaking a combination of several proteins in the complement system attaching to a pathogen and causing their cell membrane to burst, which kills the pathogen.

Protein activation cascade which is a process which greatly enhances the production of proteins in the complement system, which makes the complement system more active during larger invasions of pathogens.

All in all this system is constructed to aid and enhance the other parts of the innate immune system [30, 31].

2.3 The adaptive immune system

The adaptive immune system learns to recognize foreign invaders as we live. Vaccination is directly associated to the adaptive immune response, basically vaccination are injection of a small number of pathogens (commonly viruses) which makes it possible for the body recognise the pathogen before we get a large scale attack from that pathogen which could be lethal otherwise, since vaccination only consists of a small number (and weakened) of an otherwise lethal pathogen the immune system are able the handle the attack and thus learn to recognise the foreign invader in case a future attack, which enables the immune system to efficiently eliminate the pathogen on the next encounter[27].

The adaptive immune system works through the lymphatic system which is a large network spread through the body in which the lymphocytes circulate, much like the bloodstream but with lymphatic fluid instead of blood. The white blood cells governing the adaptive immune system are the T-cells and B-cells. Both T-cells and B-cells are lymphocytes which are found in the lymphatic fluid. T-cells and B-cells are derived from the bone marrow [10].

2.3.1 The lymphatic system

The lymphatic system consists of a network of lymph vessels and nodes which is distributed over the whole body, see figure 2.1. The lymphatic systems main function is to distribute lymphatic fluid throughout the body, beyond the lymph vessels there are large accumulation of lymphocytes in the thymus, lymph nodes, spleen and appendix which in turn are called lymphoid organs. The lymphocytes move from the lymphatic system to the bloodstream through the lymph nodes and other places where the surfaces between the lymphatic system and the blood stream allow for it. The lymphocytes continuously circulate in and out of the lymphatic system til they find a foreign invader to eliminate [10].

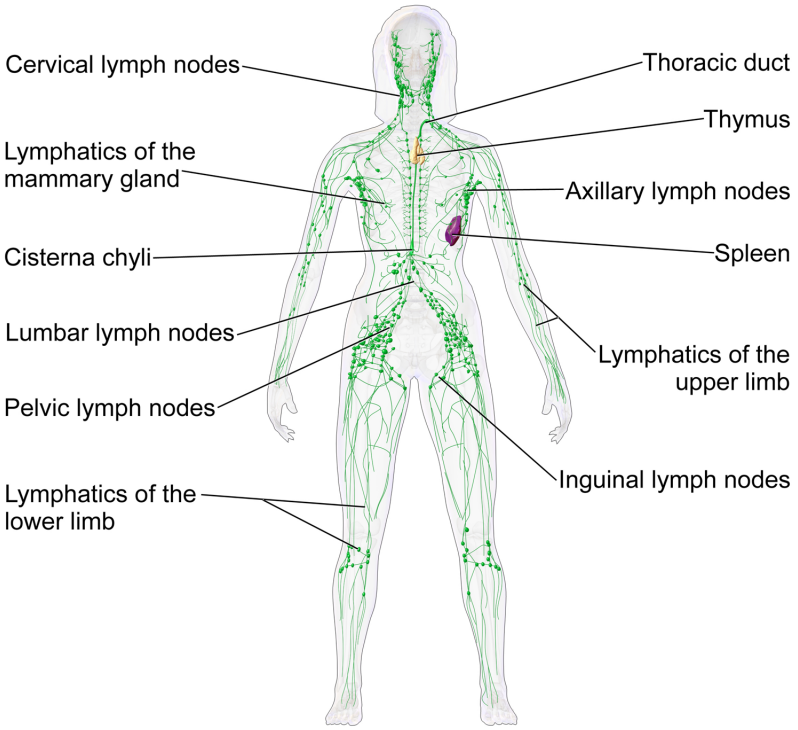

Figure 2.1: Picture of the lymphatic system and important organs which cooperates with it. Part descriptions are included on the figure. Note that lymph nodes accumulate at certain places.[Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436]

All lymphocytes have their origin from the bone marrow, the T-cells migrate to the thymus to mature (hence T-cell) and the B-cells stay in the bone marrow and mature (hence B-cell). The natural killer cells can mature anywhere in the lymphatic system including the lymphoid organs. After the lymphocytes have matured they are ready to execute their tasks [10].

There are 2×10^{12} lymphocytes in the body, which is about equal to the mass of our brain [10].

2.3.2 Recognition of foreign invaders

To understand an immune response of the adaptive immune system it is essential to understand how antigens and antibodies function and how the immune cells make use of them.

Antigens

An antigen is primarily a substance produced by pathogens outside of our own body, such as bacteria, virus or microorganisms. It's the substance that makes the immune cells separate self from non-self, for example the immune system don't want to attack the cells in our body so they doesn't contain any antigens which triggers an immune response, unless the cell is infected or dysfunctional, but pathogens on the other hand have antigens on there surface which is foreign and thus, triggers an immune response [33].

Antibodies

Antibodies are essentially proteins enabling detection of foreign cells in the body by binding to antigens attached to the surface of a pathogens or infected cells representing an antigen which is foreign. An artistic representation of an antibody is shown in figure 2.2, the antibodies are "Y" shaped with variable regions on the top of the "Y" (as seen written on text). The variable regions varies from antibody to antibody, this is because this region is suppose to bind to some kind of antigen from a foreign pathogen, and therefor the B-cell produce a tremendous amount of different antibodies, so that some of them might bind to an antigen (kind of trial and error method), the variable region must fit to the antigen much like a jigsaw in a puzzle, to trigger an immune response [34].

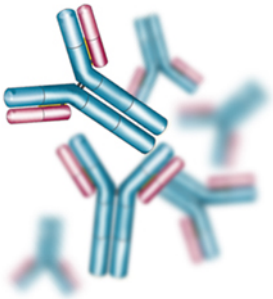

Figure 2.2: An artistic representation of an antibody. Antibodies are "Y" shaped proteins with the top of the "Y" as variable region, the black line in the middle of top of the "Y" separate the variable region (top) and the constant region. The red coloured region have no significant meaning in this report.

These proteins are produced by B-cells and are placed on the surface of the B-cells with the bottom of the "Y" to the surface making the variable region able to bind to an antigen. This trial and error method of finding a matching antibody to an antigen seems at first like finding a needle in a haystack, but remember that

there are 300×10^9[10, 35] of B-cells circulating in the body, with different antibodies. After an immune response is triggered millions of antibodies are produced and circulates freely in the blood stream and in the lymphatic system. The free floating antibodies aids the complement system by opsonization, membrane attack complexes and protein activation cascades, note that the complement system consist of more proteins than antibodies [34].

2.3.3 A immune response by the adaptive immune system

See figure 2.3 for an overlook of an immune response made by the adaptive immune system, keep this figure in mind when reading this subsection. This whole section will be based upon the sources [36, 37].

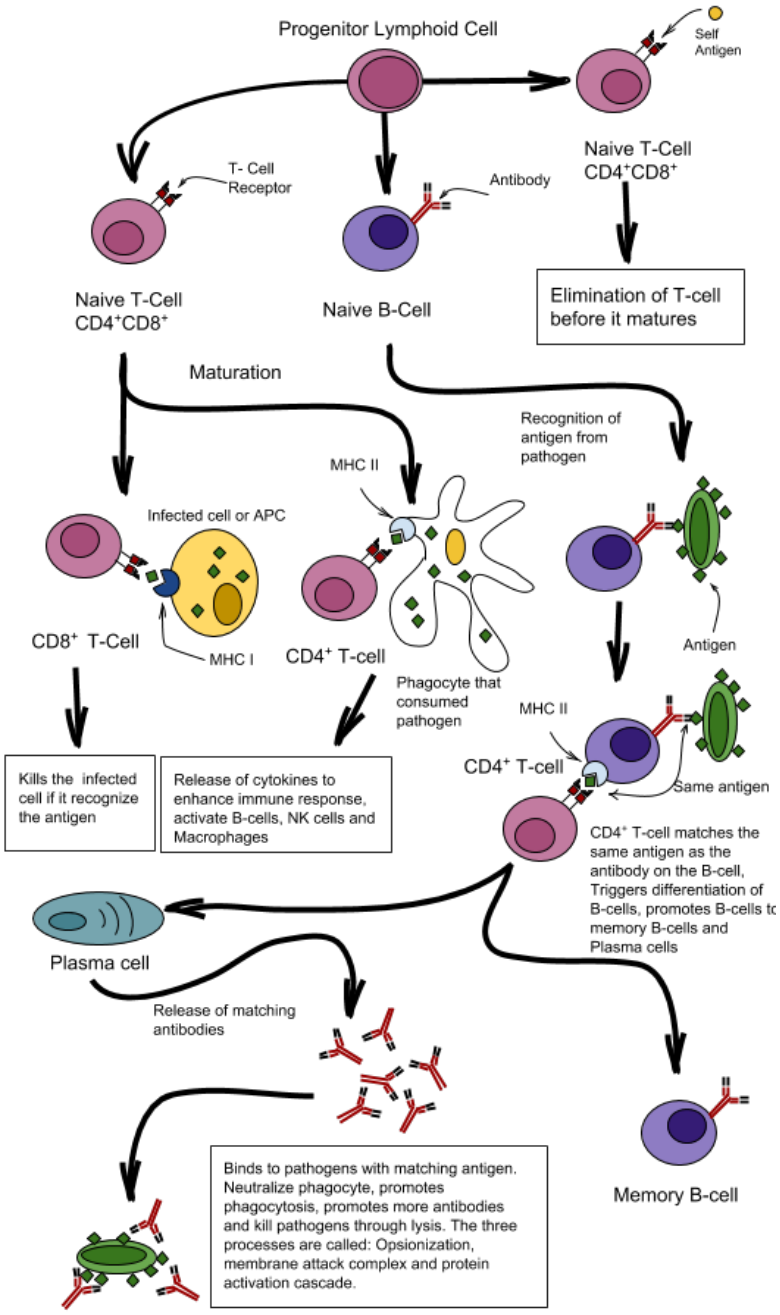

Figure 2.3: A network of events in an adaptive immune response. Note that there are more events happening in reality but this is enough to understand the main events happening in an immune response made by the specific immune system. [Picture by Lars Liberg 2019]

First of all naive T-cells and B-cells are promoted from a common progenitor lymphoid cell. The T-cells have receptors which are suppose to bind to foreign antigens, so if the receptor happens to bind to antigens of our own body (self antigens) it will be killed before it matures in order to protect our body from getting attacked by our own immune system. B-cells on the other hand are equipped with antibodies on their surface in order to find pathogens. The naive $CD4^+CD8^+$ T-cells matures in order to become $CD8^+$ T-cells or $CD4^+$ T-cells, with completely different functions.

The $CD8^+$ T-cell is cytotoxic meaning that it may kill cells with poison causing apoptosis (cell death, much like forcing the cell to commit suicide) to the cell, note that $CD8^+$ T-cells attack infected cells or antigen presenting cells, not pathogens. The $CD8^+$ T-cells detect infected cells by checking the antigen presented on cells by the major histocompatibility complex class I (MHC I) located on the cell surface. If the T-cell receptor binds to the antigen on the MHC I it releases a number of substances causing apoptosis to the cell. Recent research also proposes that memory T-cells are produced by substances secreted by activation of $CD8^+$ T-cells, which stay in the body long after the pathogen is eliminated to remember the disease, to kill the pathogen more efficiently next time it attacks the body [38].

$CD4^+$ T-cell, Th-cells or T-helper cells assist the rest of the adaptive immune response by enhancing the immune response through secretion of cytokines, causing differentiation of more T-cells and calls on natural killer cells and macrophages. T-helper cells also promote B-cells to differentiate into memory B-cells and plasma cells. $CD4^+$ T-cells becomes activated when its T-cell receptor binds to an antigen presented by an phagocyte (immune cell, e.g macrophage or dendric cell) on its major histocompatibility complex class II (MHC II) on its cell surface.

B-cells become activated after one of its antibodies binds to an antigen and at the same time have a $CD4^+$ T-cell bind to the same antigen presented on its MHC class II. After activation it differentiate to more B-cells with the same antibody and promotes to memory B-cells and plasma cells.

The Memory B-cell remain in the body a long time to remember the antibody binding to that particular antigen, so next time the pathogen with that antigen invades the body, it will be eliminated quick and efficient.

The function of plasma cells is to release a large number of free floating antibodies of the same kind as the activated B-cell had. It releases about 2000 antibodies per second.

The released antibodies then function as an aid to the complementary system. Since the antibodies are able to bind the the antigen presented by the invading pathogen, they will bind to the invading pathogens of that kind and disabling them from making any harm on the body. The free floating antibodies also promotes phagocytosis by other immune cells, and they are even able to cause lysis (pop a

hole in the cell surface, results in death) to invading pathogens through membrane attack complexes. They also promotes activation of more antibodies of the same kind. All in all these free floating antibodies aid the innate complement system.

What makes the adaptive immune response so effective is that the memory B-cells, T-helper cells and anti-bodies continuously promotes the correct T-cell receptor and antibodies, causing a chain reaction which builds up an army of specialized immune cells. When the pathogens are eliminated the promotions will cease and the supernumerary immune cells will soon die, leaving only memory cells.

2.4 How much should we eat?

Later in the results chapter comparisons between recommended energy intake and actual energy consumption will be made. Therefor this section will go through contemporary thoughts and estimations on what a human should consume. What does this have to do with the immune system? A part of this project is to map energy consumption's made by the body and see if it match up our intake, since the immune system consumes about 13.79% (table 3.3) of our total energy.

Its hard to make a proper analysis of our energy balnce with meaningful results because we all have different genetic conditions since birth, we have different heat production, digestion, body size, diet, physical activity, immune activity, health conditions and so on. So without making empirical studies in a clinical environment its hard to make any estimates that can provide us with trustworthy numbers of our energy consumption, especially in specific systems of our body, for example the immune system.

In lack of our own empirical studies we will settle with studies about basal metabolic rate, which is an approximation of energy consumption as a function of weight, height, age and sex when we are at rest, that is, without physical activity [45], plus what nutritionists recommend on the internet, which the common man are suppose to follow to maintain the same body weight, recommended calorie intake from various references is collected in table 3.7.

2.4.1 Worth mentioning about metabolism

When we eat food we extract energy from it and convert it to energy that the body can make use of, but how much of it is actually turned into useful energy? The energy expenditure is divided into three main parts, basal metabolic rate (BMR), diet induced thermogenesis and physical activity.[65]

Basal metabolic rate

Basal metabolic rate is the primary functions that require energy for us to simply stay alive. Such as heart beat, keeping the immune system active, production of new cells, energy to the central nervous system and so forth. When calculating the basal metabolic rate for a person the Harris-Benedict equation are commonly used which is described in following subsection. The definition of BMR is set to the heat production in a warm environment of an individual at complete rest, and the individual have not eaten for at least 12 hours, hence the individual is in a post absorptive state (the body have digested all food in the system) [46].

Diet induced thermogenesis

Diet induced thermogenesis (DIT) is the heatproduction generated when converting food to energy. This energy is not to any use for the body since its a resultant from breaking down the food into useful energy (except for the heat). When eating a versatile diet about 5-15 % of the energy contained in the food goes to diet induced thermogenesis in order to convert the remaining energy to useful energy that the body later may employ for physical activity, immune activity, cell generation and so forth[65].

Physical activity

It goes without saying that this energy expenditure is due to our physical activities such as a physically demanding work or exercise. The more you use your body the more energy you consume. Primarily this energy is counted as muscular energy expenditure in this report.

2.4.2 The original Harris-Benedict Equation

By multiple regressions made on 136 males, 103 females and 96 infats, J. Arthur Harris and Francis G. Benedict constructed a linear model of our basal metabolic rate (BMR). The model is called the Harris-Benedict equation and it goes

$$\text{For men: } \left(\frac{13.7516m}{1kg} + \frac{5.0033h}{1cm} - \frac{6.7516a}{1year} + 66.4730\right) kcal \tag{2.1}$$

$$\text{For women: } \left(\frac{9.5634m}{1kg} + \frac{1.8496h}{1cm} - \frac{4.6756a}{1year} + 655.0955\right) kcal \tag{2.2}$$

where m is the mass in kg, h is the height in cm and a is the age in $years$. The BMR is defined by the heat production of an individual at complete rest plus in an

post-absorbative state (not eaten in 12-14 hours) [46]. Conversion to kJ is made by multiplying with the factor $4.184\frac{kJ}{kcal}$.

Studies from 2007 suggest that the Harris-Benedict equation should be modified by adding ethnicity and weight history which have significant effect on our current BMR [47].

All in all it's hard to construct a bullet-proof formula to estimate our BMR due to our differences.

2.4.3 What should you eat in real life?

Unfortunately this simple question can't be answered in a scientific manner. All dietitians suggest different diets and tactics of eating to reach your optimal mood or well being with respect to your daily activity. This fact makes it even harder to make conclusions in this report regarding energy consumption made by different systems of the body. The only way this actually can be managed is to collect data from a number of stand-alone sources and see where we end up, scientific or not, with enough sources it will at least be statistically correct. Those numbers are presented in table 3.7.

Chapter 3

Estimations Of Energy Consumption In The Human Body And Useful Numbers

This chapter presents estimations made on energy consumption's in different systems of the body and also some other useful numbers needed to produce a results in the next chapter. White blood cell counts and other numbers in the previous chapter will be collected in the following section so that they are easy to access.

3.1 Cell count estimations and fun facts

In table 3.1 various estimations are presented, this table is mostly for fun and to give a feeling of how many cells and molecules that are active in our body. For example about 83% of our cells are red blood cells, and we actually got more bacteria in our body (most of them are located in the tract) than cells of our own body.

Table 3.1: Estimates of various data in the human body

Fun facts			
Estimation Of	Answer	Source(s)	Comment
Amount of white blood cells in the bloodstream	1%	[8]	–
Number of lymphocytes in human body	2×10^{12}	[9]	–
Number of cells in human body	3×10^{13}	[39]	Average man, 70kg
Number of bacteria in human body	3.8×10^{13}	[39]	Average Man, 70kg
Number of red blood cells in human body	2.5×10^{13}	[40, 41]	$5 \times 10^6 \times 5.2 \times 10^6$
Basal metabolic rate per day, human female	5.44-6.28 MJ	[42, 43, 44]	All sources are considered
Basal metabolic rate per day, human male	6.69 - 7.53 MJ	[42, 43, 44]	All sources are considered
Daily energy expenditure males	14 ± 2.5 MJ	[71]	62 subjects, ages 18-29

In table 3.2 the content and quantities of the white blood cells are listed. Remember that the white blood cells constitute 1% [8] of the blood in our blood stream.

Table 3.2: White blood cell components in the blood stream: The term white blood cell is a collection name of neutrophils, eosinophils, basophils, lympocytes and monocytes. This table lists the percentage that each immune cell constitutes of the white blood cells circulating in the blood stream [24]

Immune Cell	% white blood cells
Neutrophils	60-70
Eosinophils	2-4
Basophil	0-1
Lymphocytes	20-30
Monocytes	3-8

3.2 An actual estimation of where the energy goes in our body!

A few number of estimations on energy expenditure for specific systems and organs have been made by a handful of people. Mainly compiled by *Rainer H. Straub* from the following sources: [48, 49, 50], which in turn have collected data from several sources, calculations are made from energy requirements on cell level, i.e energy it takes to construct a normal protein and so forth. The main result is shown in table 3.3 below.

Table 3.3: Energy expenditure in human systems and organs per day: The energy expenditure of the liver, heart, gastrointestinal tract and skin are hard to calculate independently from the immune system. When a person is not at rest the energy expenditure for muscles and heart increases significantly. The following condition are met: awake, lying, after overnight fast, thermoneutral (no heat production due to low/high temperature), and no emotional stress, then a person weighing 80 kg and 1.80 m in height needs approximately 10,000 kJ/day (since the immune system is included in the liver and implicitly other organs/systems one can't sum the table values to get the total energy expenditure, hence approximately 10 000 kJ/day) .

System/Organ	Energy expenditure per day [kJ]
Muscels at rest	2500
Central nervous system	2500
Immune system (in quiescent state)	1600
Liver (including immune cell activity)	1600
Heart	1200
Gastrointestinal tract	620
Kidneys	600
Spleen	480
Lungs	400
Skin	100

As seen in table 3.3 the immune system is the third (or fourth) most expensive system/organ in our body with a daily expenditure of 1600 kJ. When the immune system is activated the expenditure of energy raises to approximately 2100 kJ, the muscles may consume more than 10,000 kJ/day under extreme work or exercise conditions, and the heart also consumes more energy when the muscles are used due to increased oxygen usage which require the heart to beat faster. [50].

Its important to note that these values are estimated from a person weighing 80 kgs, and 1.8 m in hight, generates no heat, have no emotional stress, have

not eaten over night, is awake and lying down. The numbers from table 3.3 are therefor calculated under very ideal conditions for an awake person at complete rest. So under normal circumstances the energy consumption are most certainly higher than those in table 3.3.

Conclusively the number used in later comparisons is 10 $000kJ$ as motivated in the table caption.

3.3 The dietitian says...

In this section we will walk through different sources on what calorie intake we are supposed to consume every day, the sources vary from governments, companies to individuals (educated dietitians). Later in the results section these numbers will be compared to measured/estimated energy expenditures to see if the world of dietitians is in agreement with the universe of science.

3.3.1 The Canadian government recommends

The Canadian government web page have an article with proper equations where age, sex, height, weight and physical activity are the input parameters. The equations are different with respect to a persons age, that is when you are a baby the equations differ from when you are a teenager which differ from an adults. Medical news today have compiled tables with "Canadas" equations for daily calorie intake which can be seen in table 3.4 and 3.5 for males and females respectively [52].

Table 3.4: Recommended calorie intake for males with respect to age and activity level: The values are supposed to be calculated for an average body size and height for each age. The energy is measured in kcal. In order to convert the estimates to kJ multiply the values by 4.184 $\frac{kJ}{kcal}$

Age	Sedentary level	Low active level	Active level
2-3	1 100	1 300	1 500
4-5	1 250	1 450	1 650
6-7	1 400	1 600	1 800
8-9	1 500	1 750	2 000
10-11	1 750	2 000	2 300
12-13	1 900	2 250	2 600
14-16	2 300	2 700	3 100
17-18	2 450	2 900	3 300
19-30	2 500	2 700	3 000
31-50	2 350	2 600	2 900
51-70	2 150	2 350	2 650
71+	2 000	2 200	2 500

Table 3.5: Recommended calorie intake for females with respect to age and activity level: The values are supposed to be calculated for an average body size and height for each age. The energy is measured in kcal. In order to convert the estimates to kJ multiply the values by 4.184 $\frac{kJ}{kcal}$.

Age	Sedentary level	Low active level	Active level
2-3	1 100	1 250	1 400
4-5	1 200	1 350	1 500
6-7	1 300	1 500	1 700
8-9	1 400	1 600	1 850
10-11	1 500	1 800	2 050
12-13	1 700	2 000	2 250
14-16	1 750	2 100	2 350
17-18	1 750	2 100	2 400
19-30	1 900	2 100	2 350
31-50	1 800	2 000	2 250
51-70	1 650	1 850	2 100
71+	1 550	1 750	2 000

3.3.2 Various wannabe fit sources

In this section various so called calorie calculators on the web are used to generate recommended calorie intake. A calorie calculator is a tool that calculates your recommended calorie intake per day, if you want to lose weight or keep your weight the same. In order to get the most of it we are going to take the average of all averages of all females and males. In table 3.6 [53] the average height and weights for females and males from different ethnicity's are shown.

Table 3.6: Average weight and height for men and women from different ethnicity's: Measurements are made from people between the ages 18 and 40, hence the average age is 29.

Ethnicity	Male		Female	
	Height [m]	Weight [kg]	Height [m]	Weight [kg]
Northern Europe	1.80	87.1	1.67	71
Central Asia	1.71	76.6	1.59	68.5
North America	1.77	90.4	1.64	77.4
South America	1.71	77.8	1.58	67.7
Central Africa	1.69	62.9	1.58	58.0
Average	1.74	78.9	1.61	68.5

Calorie calculators require age, gender, weight, height and physical activity. Height and weights are given in table 3.6, the measurements in table 3.6 are made from people between 18 and 40, hence the average age becomes 29. So when using the calorie calculators the age is set to 29, since all heights and weights are relatively similar we look at the average height and weight only, and set physical activity to sedentary to make the data easier to analyse later in the result section. The results are shown in table 3.7.

Table 3.7: Table of daily calorie intake from various calorie calculators found on the web: The unit is in calories and kJ in the brackets. At the bottom of the table an average is calculated from all sources. The values are caluculated from average height and weight for males and females worldwide between the ages 18-40. For males: height= $1.74m$, weight= $78.9kg$, age= $29years$ and physical activity= *sedentary*. For females: height= $1.61m$, weight= $68.5kg$, age= $29years$ and physical activity= *sedentary*. The average values are calculated from the data presented in table 3.6

Webb page	Male	Female	Source
Calculator.net	2 084 (8 719.5)	1 662 (6 953.8)	[54]
Healthline.com	2 084 (8 719.5)	1 662 (6 953.8)	[55]
freedieting.com	2 073 (8 673.4)	1 656 (6928.7)	[56]
Caloriecontrol.org	2 084 (8 719.5)	1 662 (6 953.8)	[57]
Active.com	2 580 (10 794.7)	2 339 (9 786.4)	[58]
Omnicalculator.com	2 084 (8 719.5)	1 662 (6 953.8)	[59]
The5-2dietbook.com	2 045 (8 556.3)	1 597 (6 681.8)	[60]
bcm.edu	2 565 (10 732.0)	1 968 (8 234.1)	[61]
bmicustom1.com	2 069 (8 656.7)	1 655 (6 924.5)	[62]
Precisionnutrition.com	2 433 (10 179.7)	1 942 (8 125.3)	[63]
Manytools.com	2 362 (9 882.6)	1 897 (7 937.0)	[64]
Average	2 224 (9 305.2)	1 792 (7 497.7)	–

Now we have data for daily energy expenditure from various "health sources" which is as average as it gets for an average built female or male. This would make the data as valid as possible in order to draw meaningful conclusion when used in the results part.

Note that some of the sources use the same method for calculating the calorie intake in table 3.7 , but since it is merely statistical it does not matter, the only important thing here is to investigate the standard of what people use to calculate their calorie intake.

Earlier in table 3.3 the energy expenditure at complete rest was estimated to be approximately 10 000 kJ/day which is slightly higher than the average of all average male from table 3.7.

Chapter 4

The Creation Of An Artificial Immune System

The second part of this master's thesis is to produce simulations of the adaptive immune response with agent based modelling, the aim is to see if any remarkable dynamics arises with the rules made in the system (i.e rules the agents in the system follow, e.g. may traverse up, down, left and right). The code itself does not contain any equations which actually would limit the results to theoretical assumptions or alike, instead reasonable assumptions about the adaptive immune response are made with respect to the theory section and some other sources of information in order to create the rules the agents follow (i.e agents are immune cells, pathogens and infected cells).

As mentioned above the code is made by agent based modelling which is generates a complex adaptive system, since the adaptive immune system is just that, it should be a good idea to use a complex adaptive system for simulating the real adaptive immune system. Although the real immune system seems infinitely complex in its complexity one must start somewhere.

4.1 Basic idea

In reality immune cells circulate and oversee all our cells like a police patrol. For practical purposes I generate a 2 dimensional grid representing cells of our own body.

Then at random I spawn viruses on that grid, which have a probability of infecting the cell at the coordinate in which it resides. Viruses may traverse up,down,left and right on the cell grid. When the virus infects a cell it gains an attribute which indicates that the cell is infected.

Infected cells can replicate and spread the disease [70] up, down, left and right

with a diffusion rate constant.

There exists cytotoxic T-cells, memory T-cells, B-cells and Th-cells. They are all assigned a number representing an antigen, that is instead of making actual antigens and receptors it should be sufficient to spawn immune cells and pathogens with a number associated with antigens, e.g. if a T-cell reside on a cell on the grid which is infected with a pathogen which is represented by number 1543, and if the T-cell have an antigen receptor associated with 1543 it triggers an T-cell activation. T-cells will react on cells on the grid, Th-cells will react on phagocytes which act as APCs with the same antigen representation as the spawned virus, and B-cells will react on the viruses invading the grid. Their random walk allow them to traverse up, down, left and right.

The immune cell activation generate 2 new immune cells of the same kind and 1 of the other two (Th-cell- and B-cell activation), except for T-cell activation which generate 2 new T-cells, one memory T-cell and one Th-cell. In contrast to the initially spawned immune cells those generated by immune cell activation have a life span. It is important so separate the initial set of immune cells and the extra immune cells generated from activation since all the extra cells will have a number associated to the correct antigen (all pathogens invading the grid have the same antigen, i.e one disease), while the initial set of immune cells keep receiving new antigen numbers (instead of dying) since their function is to find the correct antigen number by constantly producing new immune cells (with new antigen receptors), actually it would be more accurate to assign new coordinates as well but they already reside on random cells so lets save some computation time instead.

On top of all this I added constants restricting the maximum number extra immune cells allowed in the simulation (those generated from immune cell activation). This will later allow for analogies to restricted energy usage for the immune system, that is, more immune cells cost more energy to produce, what happens when energy is restricted?

The rest of the code is more or less practical execution of the assumptions mentioned above and a lot of changing to the input parameters, in order to make the system stable.

The easiest thing to get to know how it works in action is to read the code directly, its well commented and follows a relatively simple framework. The whole MATLAB code can be viewed in Appendix A.

4.2 A list of assumptions made in the code

Read the previous section for the motivations and ideas leading to the following assumptions.

- The infectious agents got passed the innate immune system, leads to a more realistic system consisting of the adaptive immune response alone, making the innate immune responses negligible.
- Cell grid is quadratic and bounded
- The initial number of immune cells on the grid is proportional to the number that exists in the whole body, i.e all cells of the body.
- Constant number of immune cells of respective kind, i.e the non activated system have a constant number of immune cells.
- 10^5 antigens and antigen receptors (should be 10^{10} but takes to long time to simulate)
- Exist phagocytes that represents the antigen carried by infectious agent. Proportional to the number of phagocytes (other than lymphocytes in the body). Actually a reasonable assumption since we assume that the infection have broken trough the innate immune defences, i.e exist a lot of phagocytes that carry the phatogens antigen, after a Th-cell finds an phagocyte, the phagocyte is killed, does not spawn any new phagocytes.
- Immune cells, phagocytes and pathogens may occupy the same cell in the system
- Random walk: each immune cell or pathogen may traverse up, down, left, right each iteration. The grid have boundaries which cannot be crossed.
- Neglect the effect of antibodies since they per definition belongs to the complementary immune system.
- It seems like memory Th cells doesn't exist in such a large number as for the cytotoxic T- cells, neglect these!
- If a T-cell is on the same coordinate as an infected cell, then there is a probability that it kill/heal the infected cell and triggers a T-cell activation.
- If a B-cell is on the same position as a virus it is a probability of B-cell activation.
- If a Th-cell is on the same position as a phagocyte it is a probability that it kills the phagocyte and trigger a Th-cell activation.
- Immune cell activations generate 2 of the same kind and 1 of the others. Except for T-cell activation which generate 2 new T-cells, 1 memory T-cell and 1 Th-cell.

- Infected cells have a diffusion rate, may spread the disease up, down, left and right.
- The immune cells which spawn from the activation (with the correct antigen receptor) have a life spawn.

4.3 Input parameters for the simulations

In total there are 23 input parameters to the code. For later analysis 19 of them are fixed, the values where determined by trial and error in order to make the system stable and to feel intuitively good with my perception. The parameters which are going to be varied in the simulations are the grid size and the maximum number of extra T-cells, B-cells and Th-cells (i.e. those spawned by immune cell activation). Appendix A constains the complete code with all function files, see appendix A.1 for an overview of all parameters, they are located on the top of the main code.

In order to make the code as realistic as can be the number of immune cells on a given grid size should be proportional to the total number of lymphocytes divided by the total cells in our body (since those numbers are available). The total number of cells in our body is 3×10^{13} [39] and the total number of lymphocytes are 2×10^{12} [9]. The lymphocytes consists of 19% T-cells, 23% B-cells and 46% for Th-cells [66]. which lead to the simple equation:

$$LymphocytesOnGrid = 2 \times 10^{12} \times proportionOfLymphocyte \times \frac{gridSize^2}{3 \times 10^{13}} \quad (4.1)$$

Where $LymphocytesOnGrid$ is the number of lymphocytes which is spawned on the grid corresponding to the proportion of that lymphocyte which is inserted into $proportionOfLymphocyte$ (T-cells, Th-cells or B-cells).

4.4 How other human beings simulates the immune system

This section is based upon chapter 3 in the book Artificial immune systems: A new Computational Approach [67].

Other people tend to reduce the simulations of the immune system to isolated mechanisms, for example, maturation time for one single immune molecule, generation of antigen receptors or number of lymphocytes with identical antigen receptors. It is also common to use EAs (evolutionary algorithms) or neural networks to adapt the system over time. They also tend to make a much more complicated

process to emulate antigens and antigen receptors, that is so they work as actual jigsaws and are suppose to be puzzled together by introduction of a shape space in which pieces are generated, e.g. [110110] fit to [001001] in a shape space with 6 dimensions where each element may assume values 0 or 1.

Several differential equations are made to describe processes. Some examples are: The pioneer model of N. K. Jerne which describes the number of identical lymphocytes (those with the same antigen), the model of J.D Farmer and collaborators which shows number of matching antigens and receptors and the model of F. Varela and A Coutino which describes antibody concentration and maturation of immune cells.

All in all the model introduced in this report tries to describe a much larger system in the immune system than usual. But people sure make the right decision to reduce the problem since the immune system is very complex and interconnected to almost everything in the whole body.

Chapter 5

Results

This section start off with a comparison of Straub et al. estimations VS. recommended calorie from a variety of sources. Then results from simulations of the adaptive immune response is shown, it regards different energy maximums set to the immune system and the time it takes to find a decease with respect to the number of exposed cells.

5.1 Nutritionists VS. science

From the estimation of energy expenditure in different organs/systems in the body made by *R.H. Straub et al.* we know that the our body use approximately 10 000 kJ/day. Lets compare this estimation to the recommended calorie intake from Canada and the various "wanna be fit" sources, and also estimations from the Harris-Benedict equations for basal metabolic rate for the average of all average male, namely $height = 174cm$, $weight = 78.9kg$, $age = 29years$, when inserting the values into the Harris-Benedict equation we get:

$$P = \left(\frac{13.7516}{1kg}78.9kg + \frac{5.003}{1cm}174cm - \frac{6.7516}{1y}29y + 66.4730\right) \times 4.184\frac{cal \times kJ}{cal} = 7641kJ \tag{5.1}$$

The comparisons are made in table 5.1.

Table 5.1: Data from Straub et al. VS. recommended calorie intake from varios sources and basal metalbolic rate calculated from the Harris-Benedict equation

Comparison	Calculation	Difference
Straub et al. VS. Canadian Government, male 19-30 sedentary	10 000kJ - 2500×4.184kJ	-460kJ
Straub et al. VS Canadian Government, male 19-30 low active level	10 000kJ-2700 × 4.184kJ	-1 296 kJ
Straub et al. VS. Wanna be fit sources males, sedentray average	10 000kJ - 9 305.2kJ	694.8 kJ
Straub et al. VS. Wanna be fit sources females, sedentary average	10 000kJ - 7 497.7kJ	2 502.3kJ
Straub et al. VS highest recommended calorie intake from various wanna be fit sources (males)	10 000kJ - 10 794.7kJ	-794.7kJ
Straub et al. VS. Harris-Benedict equations, average male	10 000kJ - 7 641kJ	2 359kJ

Note that the data estimated by *Straub et. al.* are made from a condition very close to complete rest while the data from the other sources are calorie intake estimations for a person with sedentary lifestyle which is suppose to maintain the same weight, with this calorie intake. Sedentary lifestyle in this context is that you have a work which is not physically demanding and that you do not exercise on your spare time, however you do all necessities of everyday. So sedentary here means more physical activity than the people from *Straub et al.* estimations. Spontaneously by looking at the comparison for females with sedentary lifestyle, it is enough to consider males only since the difference is to far off, comparing to the other values.

5.2 Simulating immune responses

In this section simulations are made to emulate different energy maximums and number of exposed cells. Different energy maxima are emulated through restriction of generated immune cells through activation, since its require energy from the body to produce the extra immune cells. The number of exposed cells are varied trough increasing the quadratic grid size since every coordinate emulates a cell. There are more ways to vary the system but the system is very sensitive to change, and variation in maximum energy and grid size does not affect the stability of the system, which makes it possible to analyse these parameter changes while all other parameters are fixed during the simulations.

5.2.1 Varying energy maximum

Energy maximum is represented by the number of allowed extra immune cells produced from immune cell activation. In figure 5.1 four simulation are plotted for four different energy maximas, $max = 1$, $max = 0.66$, $max = 0.5$ and $max = 0.1$. Keep in mind that the immune cells plotted are those generated by immune cell activation, and the grid size is set to 300×300.

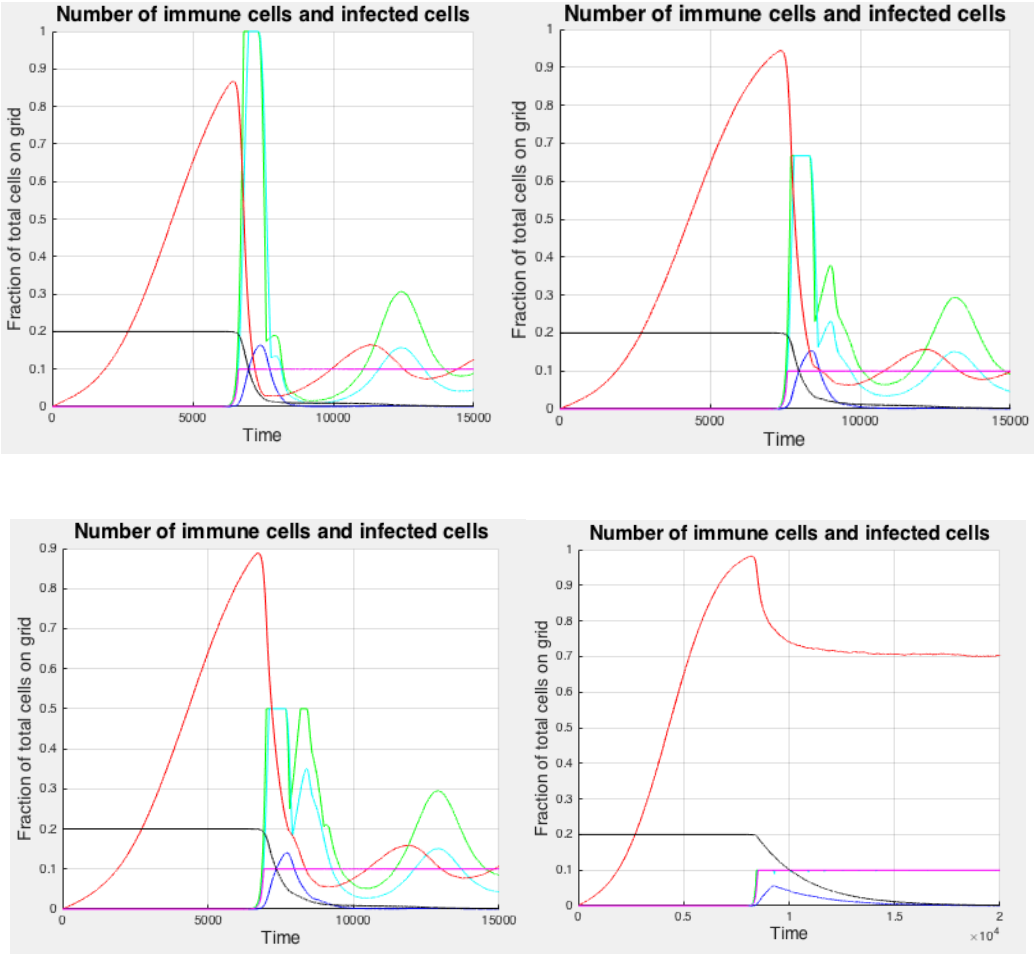

Figure 5.1: Four different energy maximas for immune cell activation. Top left: max fraction = 1, top right: max fraction = 0.66, bottom left: max fraction = 0.5, bottom right; , max fraction = 0.1. All plots include number of cytotoxic T-cells (green), B-cells (blue)- Th-cells (cyan), infected cells (red), memory T-cells (magenta) and phagocytes (black) over time. Note that only the "extra" immune cells are plotted. The grid size is fixed to 300× 300 for all cases. If the maximum allowed extra immune cells is set to 10% of the total cells on the grid, then the immune system is unable to get rid of the decease, converges to $fraction \approx 0.7$

From figure 5.1 it is clear that the three higher energy maximas have about the same dynamics, namely that it finds the decease, T- and Th-cells reaches maximum value, T- and Th-cells decrease in number, T- and Th-cells gets an extra boost and lastly T and Th-cells starts to fluctuate around $fraction = 0.1 - 0.2$. The amount of B-cells are kept relatively low, and the phagocytes are gone after they have activated enough Th-cells. The number of infected cells also behave alike in all cases, reches its peak, drops when immune cells starts to produce and lastly starts to fluctuate around $fraction = 0.1 - 0.2$

For the case $max = 0.1$ the T-, Th- and memory T-cells reaches $fraction = 0.1$ (which is the maximum allowed value for all of them) and are constant over the whole run, the number of infected drops from its peak and converges to $fraction \approx 0.7$.

5.2.2 Varying number of exposed cells

The main objective by varying the number of exposed cells is to see how fast the immune system finds the decease as a function of exposed cells. All the parameters are fixed on their standard settings for all simulations (see appendix A.1 for values), and the maximum number of allowed extra immune cells does not matter here because we are only interested in how fast it finds the decease and nothing more. The results are presented in table 5.2.

Table 5.2: Time steps til immune cells detect the decease for different grid sizes. The values are averaged over 6 simulations for all cases.

Grid Size	Time steps
300^2	8126
600^2	5298
900^2	5125
1200^2	1831
1500^2	1555

Chapter 6

Discussion

The single most annoying aspect of this works has been the lack of relevant sources which view the immune system from a physical perspective, or in terms of energy or other use-full units. Almost all sources available view it from a biological, chemical or biochemical perspective. The lack of numbers and facts lead to fewer results, the only thing I was able to produce was an overview of our body's energy expenditure as a whole, I was not able map any chemical processes in terms of energy regarding the immune system activation or anything close to that. Much more research must be made in this area from a physical perspective in order to understand what mechanisms our immune system use to work well.

The code for the adaptive immune response could be made much better and differently. First, there are 23 parameter inputs, which enable for a lot of different approaches when trying to construct a stable system. Secondly, I introduced probabilities for the immune cell activation's to happen (if they are allowed to happen) in order to retard the growth of extra immune cells. This lead to a more biological (or Gaussian) curves describing the extra immune cell populations, but it also made it almost impossible to kill all the infected cells which lead to the fluctuations in figure 5.1. This might be avoided in some way but right now I don't know how.

Introduction of antibodies and more realistic number of infectious agents (viruses in the code), currently I spawn an initial population of infectious agents and let them do their thing til they are gone. The adaptive immune response are actually only able to kill infected cells and not the free floating infectious agents, this is due to the absence of antibodies and that the innate immune system is not present. If those factors where to be added to the code it would improve the ability to emulate the real immune system. I might add that no one have done this yet by agent based models (not what I know about). The usual thing to do is to simulate a small part of some single immune process, e.g. generation of antigen receptors. People in general tend to avoid looking on the immune system as a whole, and thus

very few papers and simulations are made about this matter. I think the main issue is that the immune system hold to many mechanisms and interconnected molecules so that people give up before giving it a second thought, or that people working with immunity are totally uninterested in knowing the mechanics in physical perspective plus they don't know how to generate a code for simulation, and that the physicists lack knowledge in immunity.

The comparisons made in table 5.1 are as suspected under current circumstances. Not any remarkable results, the data fit together well despite rough estimations from straub et al. and the average of all average man inserted into 11 arbitrary calculators and averaged over all values. Obviously it is very hard to make more exact estimations due to our differences and different diets. To make the analysis more trustworthy it would require more independent estimations of energy expenditures, and that those estimations where made with respect to age, sex, height and weight, which they are not.

One might insert 180 cm and 80kgs (with age 29) into the Harris-Benedict equation, which yields 7 830 kJ/day, the average of all average was estimated to be 7 641 kJ/day, the difference is thus negligible in the context.

Chapter 7

Conclusions

7.1 About energy consumption and measured energy expenditure

Since the estimations made by *Straub et al.* and the recommended calorie intake estimated from calorie calculators both are rough estimates we can't hope for an exact match for the two. According to table 5.1 the difference between *Straub et al.* and the *Canadian government for sedentary males* the difference is 460 kJ (it deviates 4.6 % from *Straub et al.* estimations). The difference between *Straub et al.* and *"Wannna be fit" sources, sedentary males, average* is 694.8 kJ (6.9%). The rest of the values have lesser significance in the context due to physical activity, sex or less averaged.

The difference from comparing with BMR is remarkably high (2 359kJ table 5.1), this is due to different ways of measuring. BMR is calculated from heat production at complete rest and in an post-absorptive state while *Straub et al.* estimations are done by collecting data from several papers and articles using different approaches, and then the energy expenditure for organs/systems are summed together and then reduced in order to compensate for the immune systems presence in several organs/systems. Using three-dimensional positron emission tomography (3D-PET) and [18F]-2-fluoro-deoxy-glucose (FDG) is one way the expenditure of the organs and CNS is measured [51]. See reference [48] and read through the sources referenced at table 5 for a closer look if interested (the sources require knowledge beyond this report and are therefor not discussed further).

Its worth mentioning that *Straub et al.* estimations are made in a state very close to complete rest while sedentary condition from the other sources imply that you do all everyday necessities and work (not physically demanding), this leads to a reasoning that the energy calculated from these sources would be higher than the energy expenditure estimated by *Straub et al.*, in addition 5-15% of our calorie

intake goes to diet induced thermogenesis (see subsection 2.4.1). When calculating considering 5-15 % loss in calorie intake the differences become greater, calculations are shown in table 7.1.

Table 7.1: Straub et al. estimations compared to the canadian governments recomended calorie intake and the average calculated from various calorie calculators, the recommended calorie intake are reduced by the expteced loss due to diet induced thermogenesis.

Comparison	Calculation	Difference
Straub et al. VS. Canadian Government, male 19-30 sedentary	10 000kJ -2 500×4.184kJ × (100%-(5-15)%)	63 - 1 109 kJ
Straub et al. VS. Wanna be fit sources males, sedentray average	10 000kJ - 9 305.2kJ × (100% - (5-15)%)	1 160 - 2 091 kJ

From table 7.1 the highest deviation from the *Straub et al.* data is 2 091 kJ (20.91%) which is quite a difference, but as mentioned before all numbers here are rough estimates and deviations are expected. The difference from the Canadian Government is still relatively low.

In addition our estimated daily expenditure is estimated to be $14 \pm 2.5\ MJ/day$ [71] from table 3.1, which is measured from 56 male subjects between the ages 18 and 29, and of those $14 \pm 2.5\ MJ$ 1.88 ± 0.24 is spent on physical activity leaving us with $12.12 \pm 2.74\ MJ/day$ which is higher than the *Straub et al.* estimations which imply even higher deviation from the nutritionists estimations of our daily energy intake.

The final conclusion is that the numbers add up relatively good in the context which imply that *Straub et al.* and the nutritionists are on the same track from two different approaches about mans energy expenditure. But due to the significant deviation of 20.91% from table 7.1 and the estiation of $14 \pm 2.5\ MJ/day$ from [71] more research should be conducted in order to erase all doubts in this matter, namely that the energy we eat should be equal to the energy we use, since food is the only source of energy we know about.

7.2 Energy available for the adaptive immune system

From the simulations shown in figure 5.1 we get the obvious result that if the adaptive immune system have restricted access to energy it is harder to fight off a decease. The fluctuations after the first attack wave from the adaptive immune response are due to the introduction of probability of activation if T-cells reside on infected cells, in this case the probability of activation and killing the infected cell is 0.5% which make it very hard to kill exactly every infected cell before it continues to differentiate. One can also reason that the infection residues would be eliminated if the innate immune system would be present, which its not. For the bottom right picture in figure 5.1 the energy restriction was set to 10% of the grid size which made the immune cells unable fight off most of the infection which lead to an equivalent to what we call a chronic decease. The infection convergence to ~ 0.7 which is the value that appears after the constant diffusion rate stabilises with the constant number of immune cells and their ability to kill them.

7.3 How the number of exposed cells during an infection affect the time to find the correct antigen receptor to fight the infection.

Table 5.2 shows the average time (averaged from 6 simulations) for the adaptive immune response to find the correct antigen to fight the decease. By analysing table 5.2 it is easy to see that the time decreases by increasing area of exposure. This have a very simple and logical explanation, since more immune cells are allowed to patrol and try out their antigen receptors, the time it takes to find the correct antigen will decrease (tests more antigen receptors in a smaller time interval.).

Conclusively the adaptive immune system are able to trigger an immune response faster if an infection have spread to a larger surface (or volume in reality), since a larger quantity of immune cells test their antigen receptors in a shorter time.

Chapter 8

Future Work

8.1 Is the energy expenditure equal to the energy consumed?

Since there are a difference in energy expenditure and energy consumed by food according to table 7.1 especially, further research should be conducted to erase the remaining doubts that it does not add up. From table 3.1 the daily energy expenditure is estimated to be around 14 MJ/day [71] which enforces the initiative further.

I would propose to make the diets individualized in a clinical environment in order to keep the weight constant for that person, when the diet which yield constant weight is found (under the activity level set at the facility), start to measure the energy expenditure. And then repeat this study for a lot of individuals independently. There are no need to generalize the diets for a "common person" in order to check if consumed energy equals spent energy for a person, the important thing is that the numbers match exactly or at least very close for each individual studied.

8.2 Study the immune system in a holistic perspective

By reading a lot of articles about small parts of the immune system, for example how a T-cell activation is triggered, the only thing it says is what the T-cell do and what substances are released. In reality those cytokines affects many function's in the body, and thus it is very hard to make any conclusion about what mechanism it is that makes a "good" or "bad" immune system, because no one ever looks at it in a holistic view. To make it really clear I make a parable, if one only look at

the leafs on the ground how could one ever know they fell from a tree.

8.3 Improve the code or produce a code that emulates the immune system as a whole.

To improve our understanding of phenomenon in nature it is vital to describe phenomenons with mathematics, if that is to hard one can try to simulate it with a computer and then describe it with mathematics by analysing the yielded results. For the simple sake to improve human knowledge of our own body, it would be of great importance to find the mechanisms behind our immunity, it might even lead to a new kind of differential equation or function yet undiscovered.

The code introduced in this report is far from finished, introduction of antibodies would be the first improvement and then start integrating it with the functions from the innate immune system and lastly add the aspects from the complementary immune system. In other words introduce new elements until everything is included that is present in the real immune system. Then one might get some interesting results that might lead to new discoveries of how the immune system is controlled or how the mechanism of a "good" immune system works. When that is known we might be able to improve peoples immune systems so that no one ever becomes sick (in best case fantasy scenario).

8.4 Backtrack all immune cells to their origin

I have excluded that I made a try to backtrack the macrophage to its origin in order to find what is governing their quantity, but unfortunately I had no time to finish this in this thesis.

By backtracking all the immune cells one by one and chart connections between all molecules involved and important reactions, one might get insight in what it is that is enhancing or retarding our immune systems performance. Excellent future master's thesis proposal by the way.

Appendix A

Matlab codes

A.1 main

```
clc, clear all
%=========================================
%              INPUT PARAMETERS
%=========================================

%Grid set-up
gridSize = 1500; % Parameterm Squared cell scape
numberOfMaxTimeSteps = 15000; % The time the simulation
    runs
gridDim = 2; % 2D

% Immune Cell set-up, maximum number of new immune cells.
maxNumberOfExtraBCells = gridSize*gridSize; %Parameter (
    energy limit)
maxNumberOfExtraTCells = gridSize*gridSize; %Parameter (
    energy limit)
maxNumberOfExtraThCells = gridSize*gridSize; %Parameter (
    energy limit)

%Various constants
totalNumberOfLymphocytesInBody = 2*10^(12); %constant
totalNumberOfOtherPhagocytes = round((2*10^(12)
    /0.25-2*10^(12))); % constant
proportionOfThCells = 0.46; % constant
proportionOfTCells = 0.19; % constant
```

```
21 proportionOfBCells = 0.23; % constant
22 numberOfCombinations = 10^(5); % constant, number of
       different receptors and antigens
23 totalCellsInBody = 3*10^(13); % constant
24
25 %Pathogen setup
26 virusPopulationSize = 3000; % constant
27
28 %Rate in which dicease spreads cell to cell
29 diffusionRate = 0.001; % Constant, spread from cell to cell
30 infectionRisk = 0.001; % Constant, virus infects cell
31
32 %New immune cell set-up
33 updateInterval = 10; % Time steps between creation of new
       antigen receptors
34 updateFraction = 0.50; % Percent that get a new antigen
       receptor
35 maxNumberOfMemoryTCells = gridSize*gridSize/10; % Constant
36
37 %Cell death set-up
38 ageOfImmuneCells = 800; %Constant, age of the extra immune
       cells
39
40 %Chance for immune cell activation
41 probTCellActivation=0.005; % Constant
42 probBCellActivation=0.005; % Constant
43 probThCellActivation=0.005; % Constat
44
45 %=========================================
46 %                INITIALIZATION
47 %=========================================
48 hh = 0; % dummy variable.
49
50 %For the plots
51 numberOfExtraTCellsPlot = zeros(numberOfMaxTimeSteps,1);
52 numberOfExtraBCellsPlot = zeros(numberOfMaxTimeSteps,1);
53 numberOfExtraThCellsPlot = zeros(numberOfMaxTimeSteps,1);
54 numberOfInfectedCellsPlot = zeros(numberOfMaxTimeSteps,1);
55 numberOfPhagocytesPlot = zeros(numberOfMaxTimeSteps,1);
56 numberOfTMemoryCellsPlot = zeros(numberOfMaxTimeSteps,1);
```

```
57
58 % Initialize immune cells
59 gridFraction = gridSize^2/totalCellsInBody;
60
61 numberOfThCells = ...
62   round(totalNumberOfLymphocytesInBody*proportionOfThCells*
       gridFraction);
63 numberOfTCells = ...
64   round(totalNumberOfLymphocytesInBody*proportionOfTCells*
       gridFraction);
65 numberOfBCells = ...
66   round(totalNumberOfLymphocytesInBody*proportionOfBCells*
       gridFraction);
67 numberOfPhagocytes = ...
68   round(totalNumberOfOtherPhagocytes*gridFraction);
69
70 % Coordinates + antigen combination on last column
71 Th = zeros(numberOfThCells, gridDim+1);
72 T = zeros(numberOfTCells, gridDim+1);
73 B = zeros(numberOfBCells, gridDim+1);
74 phagocyte = zeros(numberOfPhagocytes, gridDim);
75
76 extraTCell = [];
77 extraThCell = [];
78 memoryTCell = [];
79 extraBCell = [];
80
81 % Initial immune cells
82 Th(:, 1:gridDim)=randi(gridSize, numberOfThCells, gridDim);
83 Th(:, gridDim+1)=randi(numberOfCombinations,
     numberOfThCells, 1);
84 T(:, 1:gridDim)=randi(gridSize, numberOfTCells, gridDim);
85 T(:, gridDim+1)=randi(numberOfCombinations, numberOfTCells
     ,1);
86 B(:, 1:gridDim)=randi(gridSize, numberOfBCells, gridDim);
87 B(:, gridDim+1) = randi(numberOfCombinations,
     numberOfBCells, 1);
88
89 % Spawn virus
90 virus = zeros(virusPopulationSize, gridDim+1);
```

```
91  virus(:, 1:gridDim) = randi(gridSize, virusPopulationSize,
        gridDim);
92  virus(:, gridDim+1) = randi(numberOfCombinations);
93
94  %Spawn phagocytes
95  phagocyte(:,1:gridDim) = randi(gridSize, numberOfPhagocytes
        , gridDim);
96  phagocyte(:,3) = virus(1, 3); % all viruses have the same
        antigen
97
98  %MAKE GRID
99  %An element on the grid equal to zero means healthy cell,
        then if infected
100 %by virus the element of the corresponing antigen will be
        assinged to that
101 %element, ie [0 0 0;0 0 10^10; 0 0 0], enables T-cells to
        cause apoptosis
102 cellGrid = zeros(gridSize,gridSize);
103
104 antigen = virus(1,3); % same antigen for all viruses!
105
106 time = 1:numberOfMaxTimeSteps; % for plot
107 %=========================================
108 %          FOR LOOP OVER ALL EVENTS
109 %=========================================
110
111   for timeStep = 1:numberOfMaxTimeSteps
112     %=====================================
113     %              RANDOM WALK
114     %=====================================
115
116     Th(:, 1:gridDim)=randomCellWalk(Th(:, 1:gridDim),
            gridSize);
117     B(:, 1:gridDim)=randomCellWalk(B(:, 1:gridDim),
            gridSize);
118     T(:, 1:gridDim)=randomCellWalk(T(:, 1:gridDim),
            gridSize);
119
120     if isempty(extraThCell) == 0
121       extraThCell(:,1:gridDim) = ...
```

```
122         randomCellWalk(extraThCell(:, 1:gridDim), gridSize)
                ;
123     end
124
125     if isempty(extraBCell) == 0
126       extraBCell(:,1:gridDim)= ...
127         randomCellWalk(extraBCell(:, 1:gridDim), gridSize);
128     end
129
130     if isempty(extraTCell) == 0
131       extraTCell(:,1:gridDim) =...
132         randomCellWalk(extraTCell(:,1:gridDim),gridSize);
133     end
134
135     if isempty(virus)==0
136       virus(:, 1:gridDim) = randomCellWalk(virus(:, 1:
              gridDim), gridSize);
137     end
138
139     if isempty(phagocyte) == 0
140       phagocyte(:, 1:gridDim) = ...
141         randomCellWalk(phagocyte(:,1:gridDim), gridSize);
142     end
143
144
145     %=========================================
146     %  Kill immune cells that are too old
147     %            Spread dicease
148     %        Immune cell activation
149     %=========================================
150     if isempty(extraTCell) == 0
151       extraTCell = KillCells(extraTCell,ageOfImmuneCells,
              timeStep);
152     end
153
154     if isempty(extraThCell) == 0
155       extraThCell = KillCells(extraThCell,ageOfImmuneCells,
              timeStep);
156     end
157
```

```
158     if isempty(extraBCell) == 0
159       extraBCell = KillCells(extraBCell,ageOfImmuneCells,
              timeStep);
160     end
161
162     cellGrid = VirusDiffusion(cellGrid, diffusionRate,
            antigen);
163
164     if isempty(virus) == 0
165       [cellGrid,virus] = SpreadVirus(cellGrid, virus,
              infectionRisk);
166     end
167
168     [cellGrid, extraTCell, extraThCell, memoryTCell]=...
169       TCellActivation(cellGrid, T, extraTCell, extraThCell,
              memoryTCell,...
170       timeStep, maxNumberOfExtraTCells,
              maxNumberOfExtraThCells, ...
171       maxNumberOfMemoryTCells, probTCellActivation);
172
173     if isempty(phagocyte) == 0
174       [extraTCell, extraThCell, extraBCell, phagocyte]=...
175         ThCellActivation(phagocyte, Th, extraTCell,
                extraThCell,...
176         extraBCell, gridSize, timeStep,
                maxNumberOfExtraBCells, ...
177         maxNumberOfExtraTCells, maxNumberOfExtraThCells,
                ...
178         probThCellActivation);
179     end
180
181     if isempty(virus) == 0
182       [extraTCell, extraThCell, extraBCell]=...
183         BCellActivation(B, extraTCell, extraThCell,
                extraBCell,...
184         virus,gridSize,timeStep, maxNumberOfExtraBCells,
                ...
185         maxNumberOfExtraTCells, maxNumberOfExtraThCells,...
186         probBCellActivation);
187     end
```

```
188 %=========================================================
189 %          PICK IMPORTANT NUMBERS
190 %=========================================================
191 if (isempty(extraBCell) == 0 || isempty(extraTCell) ==
      0 ||...
192       isempty(extraThCell) == 0) && hh == 0
193   %Sound of a gong gong when receptor connects to
        antigen the first time
194   S(1) = load('gong');
195   sound(S(1).y,S(1).Fs)
196   pause(0.1)
197   hh = 1;
198 end
199
200  numberOfExtraTCellsPlot(timeStep) = size(extraTCell,1)
       ;
201  numberOfExtraBCellsPlot(timeStep) = size(extraBCell,1)
       ;
202  numberOfExtraThCellsPlot(timeStep) = size(extraThCell
       ,1);
203  numberOfTMemoryCellsPlot(timeStep) = size(memoryTCell
       ,1);
204
205  numberOfPhagocytesPlot(timeStep) = size(phagocyte,1);
206  numberOfInfectedCellsPlot(timeStep) = nnz(cellGrid);
207
208 %=========================================================
209 %              UPDATE CELL GRID
210 %=========================================================
211 if mod(timeStep,updateInterval)==0
212 updateCellScape(cellGrid,T,Th,B,extraTCell,extraThCell,
      extraBCell,virus, phagocyte)
213 pause(0.0001)
214 end
215 %=========================================================
216 %              NEW RECEPTORS FOR
217 %                IMMUNE CELLS
218 %=========================================================
219 % Have decided that it is only necessary to generate
      new
```

```
220       %antigenreceptors, to keep the coordinates of the
              antibodies,
221       %it shouldn't make any big difference.
222
223       if mod(timeStep,updateInterval)==0
224
225         numberOfNewTCells = round(numberOfTCells*
              updateFraction);
226         numberOfNewThCells = round(numberOfThCells*
              updateFraction);
227         numberOfNewBCells = round(numberOfBCells*
              updateFraction);
228
229         T(randi(numberOfTCells, numberOfNewTCells, 1), 3) =
              ...
230           randi(numberOfCombinations, numberOfNewTCells, 1);
231         Th(randi(numberOfThCells, numberOfNewThCells, 1), 3)
              = ...
232           randi(numberOfCombinations, numberOfNewThCells, 1);
233         B(randi(numberOfBCells,numberOfNewBCells, 1), 3) =
              ...
234           randi(numberOfCombinations,numberOfNewBCells, 1);
235
236       end
237     end % end of loop over events
238
239   S(1) = load('train');
240   sound(S(1).y,S(1).Fs)
241   %% PLOTTING
242   figure(2)
243   nCells=gridSize*gridSize;
244   [~,peak]=max(numberOfInfectedCellsPlot);
245   time=1:numberOfMaxTimeSteps;
246   %peak=1; %If one wishes to see the x axis in time steps.
247   hold on
248   grid on
249   plot(time./peak, numberOfExtraTCellsPlot./nCells, 'g');
250   plot(time./peak, numberOfExtraBCellsPlot./nCells, 'b');
251   plot(time./peak, numberOfExtraThCellsPlot./nCells, 'c');
252   plot(time./peak, numberOfInfectedCellsPlot./nCells, 'r');
```

```
253 plot(time./peak, numberOfTMemoryCellsPlot./nCells, 'm');
254 plot(time./peak, numberOfPhagocytesPlot./nCells, 'k');
255
256 legend('T-cells', 'B-cells', 'Th-cells',...
257   'Infected cells', 'Memory T Cells', 'Phagocytes',...
258   'Location','northeast','NumColumns',2)
259 xlabel('Time')
260 ylabel('Fraction of total cells on grid')
261 title('Number of immune cells and infected cells')
262 hold off
```

A.2 Immune cell activation functions

A.2.1 T-cell activation

```
1  function [CellGrid,ExtraTCell,ExtraThCell,MemoryTCell]=...
2    TCellActivation(cellGrid, T, extraTCell, extraThCell,
       memoryTCell,...
3    timeStep,maxNumberOfExtraTCells,maxNumberOfExtraThCells
       ,...
4    maxNumberOfMemoryTCells, probTCellActivation)
5  %=================================
6  %  T-cell activation Set-up
7  %=================================
8  numberOfNewTCells=2;
9  numberOfNewThCells=1;
10 numberOfNewMemoryTCells=1;
11 % Letting them spawn randomly
12 % Both extra and standard T-cells may get activated!
13
14 gridSize=size(cellGrid,1);
15
16 if isempty(extraTCell)==0
17
18   numberOfExtraTCells=size(extraTCell,1);
19   for i=1:numberOfExtraTCells % For the extra T cells
20     if cellGrid(extraTCell(i,1),extraTCell(i,2))==
         extraTCell(i,3)
21       if rand(1,1)<probTCellActivation
22         for j=1:numberOfNewTCells
23           extraTCell=[extraTCell;randi(gridSize,1,1)...
```

```
24                randi(gridSize,1,1)...
25                extraTCell(i,3)...
26                timeStep];
27            end
28
29            for j=1:numberOfNewThCells
30              extraThCell=[extraThCell;randi(gridSize,1,1)...
31                randi(gridSize,1,1)...
32                extraTCell(i,3)...
33                timeStep];
34            end
35
36            for j=1:numberOfNewMemoryTCells
37              memoryTCell=[memoryTCell; randi(gridSize,1,1)...
38                randi(gridSize,1,1)...
39                extraTCell(i,3)...
40                timeStep];
41            end
42            cellGrid(extraTCell(i,1),extraTCell(i,2))=0; %Heal/
                 kill cell
43          end
44        end
45      end
46    end
47
48    if isempty(memoryTCell)==0
49      numberOfMemoryTCells=size(memoryTCell,1);
50      for i=1:numberOfMemoryTCells % For the memory T cells
51        if cellGrid(memoryTCell(i,1),memoryTCell(i,2))==
             memoryTCell(i,3)
52          if rand(1,1)<probTCellActivation
53            for j=1:numberOfNewTCells
54              extraTCell=[extraTCell;randi(gridSize,1,1)...
55                randi(gridSize,1,1)...
56                memoryTCell(i,3)...
57                timeStep];
58            end
59
60            for j=1:numberOfNewThCells
61              extraThCell=[extraThCell;randi(gridSize,1,1)...
```

```
62                randi(gridSize,1,1)...
63                memoryTCell(i,3)...
64                timeStep];
65            end
66
67            for j=1:numberOfNewMemoryTCells
68              memoryTCell=[memoryTCell; randi(gridSize,1,1)...
69                randi(gridSize,1,1)...
70                memoryTCell(i,3)...
71                timeStep];
72            end
73            cellGrid(memoryTCell(i,1), memoryTCell(i,2)) = 0; %
                 Heal/kill cell
74          end
75        end
76      end
77
78  end
79
80  for i=1:size(T,1) % For the standard T cells
81
82    if cellGrid(T(i,1),T(i,2))==T(i,3)
83      if rand(1,1)<probTCellActivation
84        for j=1:numberOfNewTCells
85          extraTCell=[extraTCell;randi(gridSize,1,1)...
86            randi(gridSize,1,1)...
87            T(i,3)...
88            timeStep];
89        end
90
91        for j=1:numberOfNewThCells
92          extraThCell=[extraThCell;randi(gridSize,1,1)...
93            randi(gridSize,1,1)...
94            T(i,3)...
95            timeStep];
96        end
97
98        for j=1:numberOfNewMemoryTCells
99          memoryTCell=[memoryTCell; randi(gridSize,1,1)...
100           randi(gridSize,1,1)...
```

```
101             T(i,3)...
102             timeStep];
103         end
104         cellGrid(T(i,1),T(i,2))=0; %Heal/kill cell
105       end
106     end
107 end
108
109 %Limit the number Of Extra Immune Cells (Energy maximum)
110 if size(extraTCell,1)>maxNumberOfExtraTCells
111   extraTCell(maxNumberOfExtraTCells:end,:)=[];
112 end
113
114 if size(extraThCell,1)>maxNumberOfExtraThCells
115   extraThCell(maxNumberOfExtraThCells:end,:)=[];
116 end
117
118
119 if size(memoryTCell,1)>maxNumberOfMemoryTCells
120   memoryTCell(maxNumberOfMemoryTCells:end,:)=[];
121 end
122
123 CellGrid=cellGrid;
124 ExtraTCell=extraTCell;
125 ExtraThCell=extraThCell;
126 MemoryTCell=memoryTCell;
127
128 end
```

A.2.2 Th-cell activation

```
1 function [ExtraTCell,ExtraThCell,ExtraBCell,Phagocyte]=...
2   ThCellActivation(phagocyte, Th, extraTCell, extraThCell,
      extraBCell,...
3   gridSize,timeStep,maxNumberOfExtraBCells,
      maxNumberOfExtraTCells,...
4   maxNumberOfExtraThCells,probThCellActivation)
5 % when Th cells are activated more Th cells with maching
    antigen receptor
6 % is produced, as well ass corresponing T-cells and B cells
7 % Does not kill any infected cells, i.e. helper cells;)
```

```
8  numberOfNewTCells=1;
9  numberOfNewThCells=2;
10 numberOfNewBCells=1;
11 nPhag1=0;
12 nPhag2=0;
13
14 antigen=phagocyte(1,3); % all phagocytes have the same
       antigen!
15
16
17 if isempty(extraThCell)==0 && isempty(phagocyte)==0
18
19   [~,iPhagocyte, iExtraThCell] = ...
20     intersect(phagocyte,extraThCell(:,1:3),'rows'); %
         matching rows
21
22   for i=1:size(iExtraThCell,1) % For the extra T cells
23     if extraThCell(iExtraThCell(i),3) == antigen
24       if rand(1,1)<probThCellActivation
25         for j=1:numberOfNewThCells
26           extraThCell= ...
27             [extraThCell;randi(gridSize,1,1) randi(gridSize
                 ,1,1)...
28             antigen timeStep];
29         end
30
31         for j=1:numberOfNewTCells
32           extraTCell = [extraTCell;randi(gridSize,1,1)...
33             randi(gridSize,1,1) antigen timeStep];
34         end
35
36         for j=1:numberOfNewBCells
37           extraBCell = [extraBCell; randi(gridSize,1,1)...
38             randi(gridSize,1,1) antigen timeStep];
39         end
40         %Does not attack the grid
41         nPhag1 = nPhag1+1;
42       end
43     end
44   end
```

```
45    % just delete some arbitrary phagocyte,
46    %but at least the correct number of them..
47    phagocyte(iPhagocyte(1:nPhag1),:) = [];
48  end
49
50  if isempty(phagocyte)==0
51    % Finding matching elements
52    [~,iPhagocyte,iThCell] = intersect(phagocyte,Th,'rows');
53    for i=1:size(iThCell,1)
54
55      if Th(iThCell(i),3)==antigen
56        if rand(1,1)<probThCellActivation
57          for j=1:numberOfNewTCells
58            extraTCell = [extraTCell;randi(gridSize,1,1)...
59              randi(gridSize,1,1) antigen timeStep];
60          end
61
62          for j=1:numberOfNewThCells
63            extraThCell = [extraThCell;randi(gridSize,1,1)...
64              randi(gridSize,1,1) antigen timeStep];
65          end
66
67          for j=1:numberOfNewBCells
68            extraBCell = [extraBCell; randi(gridSize,1,1)...
69              randi(gridSize,1,1) antigen timeStep];
70          end
71          nPhag2=nPhag2+1;
72          % Does not attack the grid
73        end
74      end
75    end
76    % delete arbitrary but correct amount..
77    phagocyte(iPhagocyte(1:nPhag2),:)=[];
78  end
79
80  %Limit the number Of Extra Immune Cells (Energy maximum)
81  if size(extraTCell,1)>maxNumberOfExtraTCells
82    extraTCell(maxNumberOfExtraTCells:end,:)=[];
83  end
84
```

```
85 if size(extraThCell,1)>maxNumberOfExtraThCells
86   extraThCell(maxNumberOfExtraThCells:end,:)=[];
87 end
88
89 if size(extraBCell,1)>maxNumberOfExtraBCells
90   extraBCell(maxNumberOfExtraBCells:end,:)=[];
91 end
92
93 ExtraTCell=extraTCell;
94 ExtraThCell=extraThCell;
95 ExtraBCell=extraBCell;
96 Phagocyte=phagocyte;
97 end
```

A.2.3 B-cell activation

```
1  function [ExtraTCell,ExtraThCell,ExtraBCell]=...
2    BCellActivation(B, extraTCell, extraThCell, extraBCell,
       virus,...
3    gridSize,timeStep, maxNumberOfExtraBCells,
       maxNumberOfExtraTCells,...
4    maxNumberOfExtraThCells,probBCellActivation)
5  % when TB cells are activated more B cells with maching
     antigen receptor
6  % is produced, as well as corresponing T-cells and Th-cells
7  % Does not kill any infected cells, i.e. helper cells;)
8  numberOfNewTCells=1;
9  numberOfNewThCells=1;
10 numberOfNewBCells=2;
11 antigen=virus(1,3); % All phagocytes have the same antigen!
12
13 if isempty(extraBCell)==0
14   [~,~, iExtraBCell] = intersect(virus,extraBCell(:,1:3),'
       rows');
15   for i=1:size(iExtraBCell,1) % For the extra B cells that
       are essential
16     if extraBCell(iExtraBCell(i),3)==virus(1,3)
17       if rand(1,1)<probBCellActivation
18
19         for j=1:numberOfNewThCells
20           extraThCell=[extraThCell; randi(gridSize,1,1)...
```

```
21              randi(gridSize,1,1) antigen timeStep];
22          end
23
24          for j=1:numberOfNewTCells
25            extraTCell=[extraTCell; randi(gridSize,1,1)...
26              randi(gridSize,1,1) antigen timeStep];
27          end
28
29          for j=1:numberOfNewBCells
30            extraBCell=[extraBCell; randi(gridSize,1,1)...
31              randi(gridSize,1,1) antigen timeStep];
32          end
33
34        end
35        %Does not attack the grid
36      end
37    end
38  end
39  [~,~, iB] = intersect(virus,B,'rows'); % matching rows
40
41  if isempty(iB)==0
42    for i=1:size(iB,1) % For the standard B cells
43      if rand(1,1)<probBCellActivation
44        for j=1:numberOfNewTCells
45          extraTCell=[extraTCell;randi(gridSize,1,1)...
46            randi(gridSize,1,1) antigen timeStep];
47        end
48
49        for j=1:numberOfNewThCells
50          extraThCell=[extraThCell;randi(gridSize,1,1)...
51            randi(gridSize,1,1) antigen timeStep];
52        end
53
54        for j=1:numberOfNewBCells
55          extraBCell=[extraBCell; randi(gridSize,1,1)...
56            randi(gridSize,1,1) antigen timeStep];
57        end
58      end
59      % Does not attack the grid
60    end
```

```
61 end
62
63 %Limit the number Of Extra Immune Cells (Energy maximum)
64 if size(extraTCell,1)>maxNumberOfExtraTCells
65   extraTCell(maxNumberOfExtraTCells:end,:)=[];
66 end
67
68 if size(extraThCell,1)>maxNumberOfExtraThCells
69   extraThCell(maxNumberOfExtraThCells:end,:)=[];
70 end
71
72 if size(extraBCell,1)>maxNumberOfExtraBCells
73   extraBCell(maxNumberOfExtraBCells:end,:)=[];
74 end
75
76 ExtraTCell=extraTCell;
77 ExtraThCell=extraThCell;
78 ExtraBCell=extraBCell;
79 end
```

A.3 Other functions

A.3.1 Infect grid function

```
1 function CellGrid=...
2   InfectGrid(cellGrid, InfectedCell,antigen)
3
4 % FUNCTION FOR VIRUS DIFFUSION.
5 % THIS FUNCTION SPREAD THE DICEASE FROM CELL TO CELL
6
7 % InfectedCells are in vector form from the function find
    in the cellGrid
8 % 3rd element in virus is the antigen combination which is
    spreading
9 gridSize=size(cellGrid,1);
10 position=zeros(4,1); % neighbors
11
12 I=[];
13 II=[];
14
15 position(1)=InfectedCell-1;
```

```
16 position(2)=InfectedCell+1;
17 position(3)=InfectedCell-gridSize;
18 position(4)=InfectedCell+gridSize;
19
20 for i=1:size(position,1) %Boundary conditions
21   if position(i)<1
22     I=[I i];
23   end
24
25   if position(i)>gridSize*gridSize
26     I=[I i];
27   end
28
29   if mod(InfectedCell,gridSize)==0 % These two must be here
       !
30     I=[I 2];
31   end
32
33   if mod(InfectedCell,gridSize+1)==0
34     I=[I 1];
35   end
36
37 end
38 position(I)=[];
39
40 for i=1:size(position,1) % Finding already infected cells
41   if cellGrid(position(i))>0
42     II=[II i];
43   end
44 end
45 position(II)=[];
46
47 if isempty(position)==0
48   r=randi(size(position,1)); % randomize the valid
       positions thats left
49   cellGrid(position(r))=antigen;
50 end
51 CellGrid=cellGrid;
52 end
```

A.3.2 Kill immune cells function

```
function Cells =KillCells(cells,ageOfImmuneCells,timeStep)
% kill all selected cells
% Selected cells are
k=find((cells(:,4)-(timeStep-ageOfImmuneCells))<0);
cells(k,:)=[];

Cells=cells;
end
```

A.3.3 Random cell walk function

```
function newCoordinates=RandomCellWalk(agentCoordinates,
    gridSize)
% Agents are either immune cells or phatogens, NOTE only
    Coordinates
gridDim=size(agentCoordinates,2);

randomWalk=randi(3,size(agentCoordinates,1),gridDim)-2;
newAgentCoordinates=agentCoordinates+randomWalk;

k=find(newAgentCoordinates>gridSize);
k2=find(newAgentCoordinates<1);

%Can't go out of bounds!
newAgentCoordinates(k)=newAgentCoordinates(k)-1;
newAgentCoordinates(k2)=newAgentCoordinates(k2)+1;

newCoordinates=newAgentCoordinates;
end
```

A.3.4 Spread virus function

```
function [CellGrid,Virus]=SpreadVirus(cellGrid,virus,
    infectionRisk)
%made for 2D cellgrids
randomVector=rand(size(virus,1),1);
k=[];
for i=1:size(virus,1)
  size(virus,1);
  if randomVector(i)<infectionRisk
```

```
8       cellGrid(virus(i,1),virus(i,2))=virus(i,3);
9       k=[k i];
10    end
11  end
12  virus(k,:)=[]; %occupy the cell grid instead
13  CellGrid=cellGrid;
14  Virus=virus;
15  end
```

A.3.5 Update cell environment function

```
1   function UpdateCellScape(cellGrid,T,Th,B,extraTCell,
        extraThCell,extraBCell,virus,phagocyte)
2       [xCell,yCell]=ind2sub(size(cellGrid),find(cellGrid>0));
3       clf;
4       sz=30; %Size of immune cells
5       hold on;
6       axis([1 size(cellGrid,1) 1 size(cellGrid,2)])
7       scatter(xCell,yCell,'r','filled');
8       set(gca,'color',[1 1 0.6])
9       scatter(phagocyte(:,1),phagocyte(:,2),4,...
10                          'MarkerEdgeColor',[0 0 0],...
11                          'MarkerFaceColor',[1 1 0]);
12      scatter(T(:,1),T(:,2),sz,...
13                          'MarkerEdgeColor',[0 0 0],...
14                          'MarkerFaceColor',[1, 0.0784,
                              0.5765]);
15      scatter(Th(:,1),Th(:,2),sz,...
16                          'MarkerEdgeColor',[0 0 0],...
17                          'MarkerFaceColor',[1, 0.4118,
                              0.7059]);
18      scatter(B(:,1),B(:,2),sz,...
19                          'MarkerEdgeColor',[0 0 0],...
20                          'MarkerFaceColor',[0.5940, 0.2840,
                              0.6560]);
21
22      scatter(virus(:,1),virus(:,2),sz,...
23                          'MarkerEdgeColor',[0 0 0],...
24                          'MarkerFaceColor',[0 1 0]);
25
26      if isempty(extraTCell)==0
```

```
27      scatter(extraTCell(:,1),extraTCell(:,2),sz,...
28                              'MarkerEdgeColor',[0 0 1],...
29                              'MarkerFaceColor',[1, 0.0784,
                                    0.5765]);
30      end
31      if isempty(extraThCell)==0
32      scatter(extraThCell(:,1),extraThCell(:,2),sz,...
33                              'MarkerEdgeColor',[0 0 1],...
34                              'MarkerFaceColor',[1, 0.4118,
                                    0.7059]);
35      end
36      if isempty(extraBCell)==0
37      scatter(extraBCell(:,1),extraBCell(:,2),sz,...
38                              'MarkerEdgeColor',[0 0 1],...
39                              'MarkerFaceColor',[0.5940, 0.2840,
                                    0.6560]);
40      end
41      hold off;
42  end
```

A.3.6 Virus diffusion function

```
1  function CellGrid = VirusDiffusion(cellGrid, diffusionRate,
       antigen)
2
3  k = find(cellGrid>0);
4  random = rand(size(k,1),1);
5  I = [];
6
7  for i = 1:size(k,1)
8    if rand(1,1) < diffusionRate
9      cellGrid = InfectGrid(cellGrid, k(i),antigen);
10   end
11 end
12
13 CellGrid = cellGrid;
14 end
```

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