

Modeling of the Immune System Using Prey and Predator Model

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Abstract — The purpose of this paper is to propose a novel mathematical model of the immune system using prey and predator method. The immune system is a complex dynamical system which can be observed from various perspectives. Specifically in this paper we analyze the reaction between antibodies, antigens and other types of cell, named defense-killer cells, which play key role in the immune response. The model for the immune system presented in this paper is based on well known mathematical tool – differential equations. The solutions of the system of equations will give us data which can be used for computer simulation of the immune system response against different pathogen organisms. By changing and adjusting the parameters of the model, we can simulate different types of attacks of various types of pathogen organisms and we can see how the patient organism will response to that pathogen without really using a live subject for the experiment.

Keywords — Immune system, differential equations, Prey and Predator mathematical model, antibodies, antigens and defense-killer cells

I. INTRODUCTION

The immune system is an amazing defense mechanism that over the years has been inspiration to many scientists who have tried to model it. It represents an inexhaustible source for many different researches in the area of immunology, bioinformatics and computer science. This mechanism is composed of many different layers of protection and involves multiple organs and different cell types. In this paper we consider the immune system as a dynamical system which changes over time. Because of the complexity of the immune system and the wide range of processes that are involved in its function, we concentrate only on one part of the immune system response- the reaction between antibodies, antigens and other types of immune system cells, defense- killer cells. We are interested in the representation of the sizes of the populations of the previously mentioned three types of cells as a function of time. The method used to construct this model is based on one concrete model of interchanging populations - the Prey and predator model. This model describes the interaction of four species, species of antibodies, antigens,

defense-killer cells and antigen-antibody complex. When these four species interact the population dynamics of each species is affected in a prey and predator way. The dynamics of the population interchange is represented by a system of four differential equations, whose solutions give the answers to our problem.

II. DEFINITION OF THE MODELING PROBLEM

The purpose of this paper is modeling the reaction between antigens, antibodies, defense-killer cells and antigen-antibody complex. The first step, as in every modeling process, is defining the sector from reality that we want to model and exploring the laws that govern that process. In order to do that, we will define the basics of the immune system.

A. Biological basics of the immune system

The immune system can be seen as a form of a defense network composed of various cells, tissues, and organs that work together to defend the body against attacks by “foreign” invaders. Those “foreign” invaders, known as pathogen organisms, can be microbes—tiny organisms such as bacteria, parasites, and fungi that can cause infections or viruses [4]. Most of the time, this system is remarkably effective, but sometimes, it loses the battle.

The two main types of immunity are nonspecific and specific immunity. Nonspecific immunity is provided by the barriers of the skin and mucous membranes lining the lungs and gut. Specific immunity activates when microorganisms evade the non-specific defenses and invade the body.

This paper is about the mechanism of the specific immunity.

The main function of the immune system is to develop the concept of distinguishing “self” from “non-self” and by doing so to eliminate all other pathogen organisms.

The secret to the success in achieving that function is in the collaboration of millions cells which are divided in various types, each type with a specific function. Any action of the immune system against a pathogen organism is known as immune response. In order to explain the concepts of the immune response, first we have to define the key players in that process.

B. Cells of the immune system

The immune system is equipped with an arsenal of cells that have different roles in the battle against pathogen organisms.

In the next parts we give a short description of the cells involved in immune system response.

a) Antigens

Anything that can trigger an immune system response is called an *antigen*. It can be a virus, bacteria, microorganism parasite such as fungi or anything that carries non-self markers and acts like a foreign body to the organism [4].

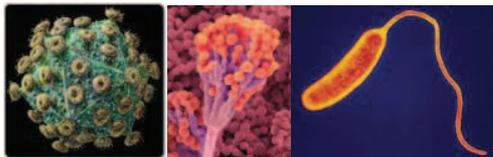


Fig 1. Different types of antigens, virus in the left picture, fungus in the middle picture, bacterium in the right picture

b) Antibody

Antibody is a special type of protein connected to the immune system that is called immunoglobulin or Ig. Antibodies are powerless when it comes to destruction of antigens because they have completely different role in the immune response process. They serve as marker molecules that bind to antigens, marking them so the immune defense system cells can destroy them.

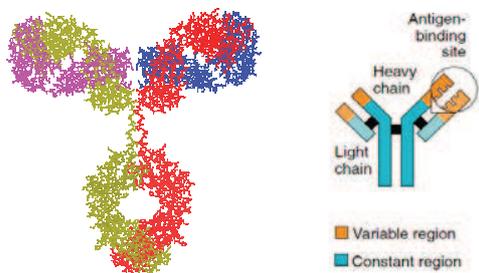


Fig 2. Antibody and antibody's structure

Antibodies are produced in response to the invasion of foreign molecules in the body by special type of immune system cell - B cell. They have characteristic shape as the letter Y, composed of two heavy chains and two light chains. The variable region, which differs from one antibody to the next, allows an antibody to recognize its matching antigen [4].

c) Antigen-antibody complex

Antigen-antibody complex, also known as an immune complex, occurs from the bonding of an antibody to an antigen. After an antigen-antibody reaction, the immune complexes cause the response of the defense cells.

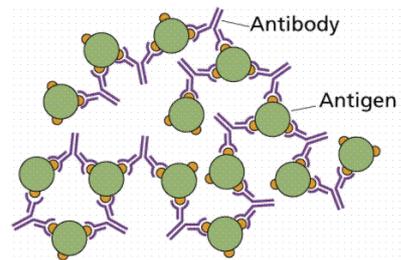


Fig 3. Antigen-antibody complex

d) Defense cells

The arsenal of the immune system is composed of various types of cells. In this paper this cells are grouped in one category called defense-killer cells. The job of the defense-killer cells is to recognize the antigen-antibody complex and neutralize the threat by destroying the pathogen organism. This category of cells includes T-killer cells, macrophages, dendritic cells, natural killer cells.

C. Description of the modeling process

Before we give the mathematical representation of the problem we must describe the process that is being modeled. In this paper we will give a very simplified, abstract and restricted version of the immune system response that is not connected to a specific pathogen organism attack.

The process can be best represented schematically, as shown on Fig 4.

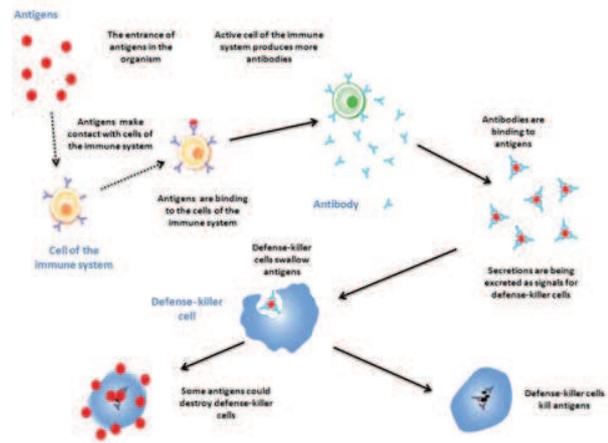


Fig 4. Schematic description of the immune response mechanism that is subject of our modeling process

Antigens enter the organism and encounter immune system cells. Immune system cells, B-cells, recognize the antigens and work by secreting antibodies in the organism. As it was previously mentioned, antibodies serve as markers to defense – killer cells to mark the antigen organism that should be destroyed. Antibodies bind to antigens and form antigen-antibody complex. The presence of antibodies triggers the immune system to create more and more defense-killer cells.

Defense-killer cells recognize the antigen-antibody complex and try to neutralize it by swallowing and destroying it. But sometimes antigens succeed in their mission, and destroy the defense-killer cells.

III. MODELS OF THE IMMUNE SYSTEM AND RELATED WORKS

Describing a realistic model of the immune system has been a challenging job for many researchers in the field of bioinformatics and immunology over the years. The complexity of the system itself has led researchers to concentrate only on a concrete part specific to the problem of the immune system that they want to explore and try to give as much as precise model of that process as they can. To accomplish that, researchers use various methodologies. An enhanced parabolic ODE system for modeling tumor invasion is used in [6]. Differential equations are also used in modeling of virus (HIV) multiplication in [7]. Cellular automata and agent-based models, that are more flexible than ODE models and offer modeling possibilities close to biologic reality are proposed in [8].

In [5] there is an interesting classification of the types of methodologies that are used for modeling the immune system.

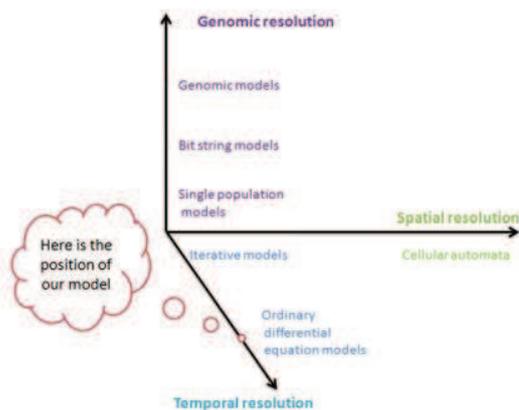


Fig 4 Schematic view of the potential resolution in different dimensions of an immune system model described in paper [5].

This paper is based on temporal resolution because the process that we describe is process that changes over time and we use the well known mathematical tool, ordinary differential equations (ODE), to model the dynamics of the populations in time.

There are also other types of classifications of mathematical models. As it is described in [5], there are two main kinds of mathematical models, descriptive and analytical models. The descriptive models aim to fit biological data, and generate mathematical constants within a defined experimental setup in order to achieve prediction through a statistical model calibration. The analytic models, as the model used in this paper, which are based on systems of ordinary differential

equations (ODEs), take into consideration the mechanisms involved in the studied system, and for which accuracy and predicting power are sacrificed in favor of abstract concepts. A famous example of the latter models is the Lotka–Volterra model for predator/prey interactions and that model is the model that is the basis of the model that is described in this paper.

IV. PREY AND PREDATOR MODEL OF THE IMMUNE SYSTEM

Prey and predator model is a well known model for representing the dynamics of the interaction of different populations. More about prey and predator model the reader can find in [1] and [2]. In the following subsections, we will shortly define the populations covered by our model, the assumptions that it is based on, and the model itself.

A. Defining the populations

First step in creating prey and predator model is defining the populations whose interaction we want to explore. Also we have to determine the type of the population i.e. which is the prey population and which is the predator population.

The populations that play part in our model are:

- 1) *Population P*: cells of antigens (or pathological microorganisms), representing the prey population.
- 2) *Population A*: population of protein molecule markers – antibodies, which is also prey population.
- 3) *Population K*: population of defense-killers cells, which can be T-killer cells, macrophages, dendritic cells, natural killer cells, i.e. predator population.
- 4) *Population C*: population of antigen-antibody complex molecules, formed by binding the antigen with the antibody.

B. Assumptions

The goal of mathematical modeling is to make model that is as simple as possible and only as complex as necessary. In order to comply with that goal, some assumptions are made.

- 1) Cells of the immune system are roughly divided into two types of cells, cells of the immune system and defense-killers cells. In reality there are different types of cells of the immune system that play different roles in the defense process.
- 2) Antigens can only be killed by defense-killer cells in the process of making antigen-antibody complex.
- 3) Antibodies cannot die by themselves. They are also killed in the process of making antigen-antibody complex.
- 4) Defense-killer cells are mortal.
- 5) In reality the first attack of an antigen is different from any other attack. In our model this fact is ignored.
- 6) This model is a general model which is not connected to a particular pathogen organism.

C. Mathematical model

The mathematical model is given by the following 4 differential equations, given in (1)

$$\begin{aligned}
 \frac{dP}{dt} &= \underbrace{m_p P}_{\text{antigens proliferation}} - \underbrace{d_p PA}_{\text{death by binding with antibodies}}, & P(0) &= P_0 \\
 \frac{dA}{dt} &= \underbrace{m_A A}_{\text{antibodies proliferation}} + \underbrace{s_A PA}_{\text{stimulation by antigens}} - \underbrace{d_A C}_{\text{death by creation of antigen-antibody complex}}, & A(0) &= A_0 \\
 \frac{dK}{dt} &= \underbrace{m_K K \left(1 - \frac{K}{N}\right)}_{\text{defense killer cells proliferation}} + \underbrace{s_k AK}_{\text{stimulation by antibodies}} + \underbrace{s_c CK}_{\text{stimulation by antigen-antibody complex}} - \underbrace{d_k KP}_{\text{death by antigens}}, & K(0) &= K_0 \\
 \frac{dC}{dt} &= \underbrace{d_{ap} PA}_{\text{antigen-antibody binding and antibody-antibody complex creation}} - \underbrace{d_A CK}_{\text{death by defense killer cells}}, & C(0) &= C_0
 \end{aligned}
 \tag{1}$$

D. Variables and parameters of the model

This model uses *variables* to describe state of being of individuals in the populations. More concretely, the main variable here is time, t. Every other variable here depends on time. P, A, K and C represent the number of individuals in the populations of antigens, antibodies, defense-killer cells and antigen-antibody complex respectively. They change with time, so they are represented as functions of time.

TABLE I
VARIABLES OF THE MODEL AND THEIR MEANING

Variable	Meaning	Dimension
t	Time	T
P	Number of individuals in the population of antigens	ℵ
A	Number of individuals in the population of antibodies	ℵ
K	Number of individuals in the population of defense-killer cells	ℵ
C	Number of individuals in the population of antigen-antibody complex	ℵ

Parameters incorporated into the equations of (1) represent fundamental quantities such as rate of proliferation, rate of destruction, rate of stimulation and some constants representing initial numbers of population's sizes. A specific kind of constant is N, which is the caring capacity of the attacked organism. It represents the limit point of reproduction of the defense killer cells in the host organism. They cannot proliferate indefinitely. Rates of proliferation, m_p , m_A , m_K represent the reproduction of the individuals of populations of antigens, antibodies and defense-killer cells respectively. Rates of destruction d_p , d_A , d_K , d_{AP} represent the rate of death of antigens, antibodies and defense-killer cells. Stimulation rate, or the rate of which some cells or substances stimulate the secretion of another cell or substance, or in the model written as m_p , m_A , m_K , represent the stimulation rates of antigens,

antibodies and defense-killer cells. Antigens stimulate the secretion of antibodies. Antibodies stimulate the secretion of defense-killer cells. Another parameters that we have to mention here, and also include in our model, are the initial sizes of the populations, i.e. initial number of individuals in the previously mentioned populations.

All of these parameters are constants which are greater than zero.

These parameters are constants that nonetheless could be and should be changed. Actually, they give the soul of this model. By experimenting with different values of these parameters, we can simulate various kinds of attack of different pathogen organisms and we can become aware of the outcome of that attack. So for every disease, by experimenting with the values of these parameters we can find those values that are best suited for that disease and we can successfully and artificially simulate the attack of that disease, which will give us data that can help researchers in finding a cure or vaccine for that disease.

A short summary of the parameters and their meanings is given in Table 2.

TABLE II
PARAMETERS OF THE MODEL AND THEIR MEANING

Parameter	Meaning	Dimension
m_p	rate of proliferation of antigens	T^{-1}
m_A	rate of proliferation of antibodies	T^{-1}
m_K	rate of proliferation of defense-killer cells.	T^{-1}
N	constant which represents the carrying capacity of the organism	ℵ
d_p	rate of destruction of antigens	$T^{-1} \ell^{-1}$
d_A	rates of destruction of antibodies	$T^{-1} \ell^{-1}$
d_k	rate of destruction of defense-killer cells	$T^{-1} \ell^{-1}$
d_{ap}	rate of binding of antigens and antibodies	$T^{-1} \ell^{-1}$
s_A	rate of stimulation of antibodies by antigens	$T^{-1} \ell^{-1}$
s_k	rate of stimulation of defense-killer cells by antibodies	$T^{-1} \ell^{-1}$
s_c	rate of stimulation of antibodies by antigen-antibody complex	$T^{-1} \ell^{-1}$
P_0	initial number of individuals in the	ℵ

A_0	population of antigens	∞
	initial number of individuals in the population of antibodies	
K_0	initial number of individuals in the population of defense-killer cells.	∞
C_0	initial number of individuals in the population of defense-antigen-antibody complex cells.	∞

V. RESULTS

In order to analyze the model, we choose to run set of experiments using predefined values for the parameters of the model. These experiments are not based on real data. At this point of this research, these experiments serve for demonstration purposes only. Experiments with real data and real simulations are intended as future work in this research.

In the sequel we will demonstrate one of our experiments.

If we choose these values for the parameters:

$m_p=0.8$; $d_p=0.5$; $m_A=0.01$; $s_A=0.8$; $m_k=0.9$; $N=10$; $s_k=0.5$; $s_c=0.1$; $d_k=0.2$; $d_{AP}=0.5$; $d_A=0.6$; $P_0=7$, $K_0=13$, $A_0=9$; $C_0=0$ in the time interval of $[0,2]$ time units, we get the results represented in Fig 2.

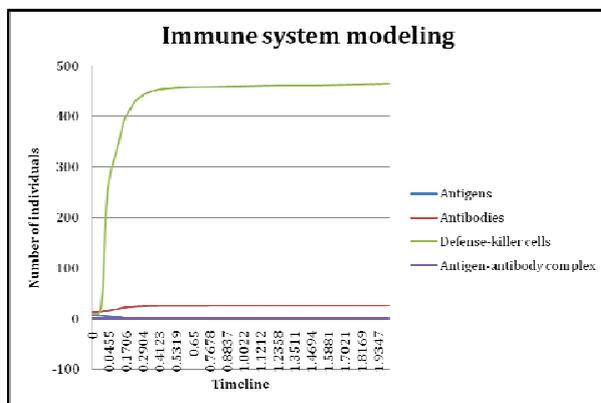


Fig 5. Snapshot of the solution of the system (1) for the previously mentioned parameters.

Here we can see that the population sizes of antigens and antibody-antigen complexes decrease as time increases, and the size population of defense-killer cells rapidly increases for some time interval and then it stabilizes. The number of antibodies cells slowly increases in the beginning and afterwards it stays constant. This simulation demonstrates a successful immunological defense reaction, where the pathogen organism is defeated.

VI. FUTURE WORK

The first thing that we can say for this paper is that is in its infancy phase. What we can further do is to try to make the model more realistic by eliminating some of the assumptions, like for example assumptions number 1 and 5 in assumption sections. In this paper all cells that participate in the immune system defense response are grouped in one population-population of defense-killer cells. In reality every type of cell from the defense-killer cells has its own specific function which could be incorporated in the model. Also, we ignore the number of the attack. In reality, for some diseases the first attack is different from every other attack, and for some diseases, like AIDS, caused by HIV virus, there is no secretion of antigens, which causes this immunodeficiency disease. Also another improvement should be done in the experiment phase of this research. Experiments and simulation have to be done using real data.

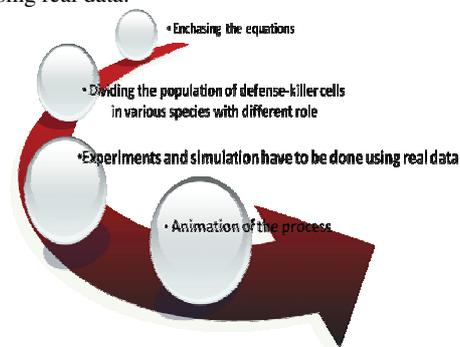


Fig 5 Future works of the model of the immune system

This model includes fifteen parameters. By using the method of non-dimensionalization we can reduce the number of the parameters and we can transform our equation in a simpler form of the equations of system (1) which will facilitate the computation of the solutions.

Finally, the most important thing that needs to be done to make this model applicable is the animation and simulation of the process of the immune system response mechanism.

VII. CONCLUSION

This paper defines a mathematical model for the process of immune system defense reaction. It is a general model, which follows various assumptions and limitations. The method which is used is Prey and Predator model for modeling interaction dynamics of the populations of antigens, antibodies and defense- killer cells. In order to make the model simpler, but also complex enough, some assumptions are made. There are still some issues that have to be considered in order to improve the model, such as not neglecting the fact in assumption number 5, which is left as a future work of research. This model can be used for simulation processes because by changing and adjusting the parameters of the model, we can simulate different types of attacks of various types of pathogen organisms. By doing so we can see how the

patient organism would response to that pathogen without really using real patient for the experiment. Another convenient use of this model is in fact that we can use it in theoretical researches to simulate drug treatment for a specific disease and vaccination programs.

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