AN INSIGHT INTO THE IMMUNE SYSTEM AND ITS MATHEMATICAL MODELS RELATING TO CYBER DEFENSE SYSTEMS

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ABSTRACT

The article has two goals: to attract the interest of mathematicians to immunology and to look for ideas for Cyber Defense Systems considering the human immune system as a highly sophisticated defense system against any dangers. An overview of the role of lymphocytes in the immune system (IS), the main IS models, and a few tips for IS mathematical modeling are given. As a future work in immunology, melanoma is considered, and relating to cyber defense the experience of the U.S. Army Cyber Command is mentioned.

KEYWORDS

Immune System, Mathematical Modeling, Melanoma, Cyber Defense System

1. INTRODUCTION

The article has two goals: the first is to attract the interest of mathematicians to immunology (there is already a lot of work done, but new experimental data and therefore many unanswered questions have arisen to generate the need for new models in immunology), and the second is to look for ideas for the Cyber Defense Systems considering the human immune system as a highly sophisticated defense system against any dangers. This complex system could inspire cybersecurity experts to develop better security systems and new intrusion detection methods using an artificial immune system for cyber security needs.

Both research fields are scorching topics nowadays. Google Scholar gives 1,240,000 links to the "immune system mathematical models" question and 17,000 links since 2020. The study of the artificial immune system has developed even faster – 54,400 links since 2020 (between 304,000 links on the immune system in total).

Let's give some background information. The immune system (IS) is a vast network of organs, white blood cells, proteins (antibodies), and chemicals. This system protects the body from bacteria, viruses, parasites, and fungi that can cause infections, diseases, and illnesses. IS contains two parts: the innate and adaptive immune systems. The innate immune system is the broad first response to a foreign substance in the body. The adaptive immune system is a second-order immune response, which is a specific, targeted response to the release of a pathogen.

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In the following: Section 2 – how immunology starts, Sections 3 and 4 – on lymphocytes, Sections 5, 6, and 7 – on IS, the main IS theories, and IS mathematical models. Melanoma as a future work (Section 8) and some ideas for Cyber Defense Systems (Section 9) are considered.

2. THE SUNRISE OF IMMUNOLOGY

Ilya Mechnikov (1845-1916) is best known for his pioneering research in immunology. He and Paul Ehrlich (1854-1915) – a German medical scientist – were jointly awarded the 1908 Nobel Prize in Physiology or Medicine "in recognition of their work on immunity" [1]. Working at the Bacteriological Institute, Odessa (1886–87), and at the Pasteur Institute, Paris (1888–1916), Mechnikov contributed to many important discoveries in the field of immune response. His most notable achievement was the recognition that phagocytes are the first line of defense against acute infection and that phagocytes are a type of white blood cell. In 1887, he noticed that white blood cells were attracted to certain bacteria. This work formed the basis of Metchnikov's cellular (phagocytic) theory of immunity (1892) and coined the term "pathogen". This hypothesis generated much resistance, especially from scientists who supported the so-called humoral theory of immunity and argued that only body fluids and blood solubles (antibodies). Although the humoral theory held sway for the next 50 years, in the 1940s scientists began to reconsider the role of cells in fighting infection.

The hypothesis developed by Paul Ehrlich [2], to explain immunological phenomena, was a side chain theory that described how antibodies, protective proteins produced by the immune system, are formed and how they react with other substances. Ehrlich postulated that each cell has on its surface several side chains or receptors that function by attaching to specific food molecules (Figure 1). This theory about antibodies and cell surface receptors is working till nowadays.

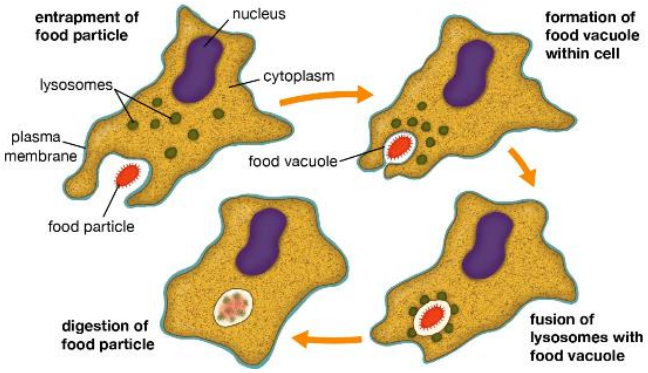

Figure 1. Digestion process

Each side chain interacts with a specific nutrient (similar to how a key is inserted into a lock), it can also interact with other molecules, such as antigens (disease-causing toxins) produced by an infectious agent. Once the toxin binds to the side chain, the interaction is irreversible and blocks subsequent binding and nutrient uptake. The body then tries to overcome this obstacle by producing large numbers of replacement side chains—so many that they cannot fit on the cell surface and are instead secreted into the circulation. The body then tries to overcome the obstacle by producing large numbers of replacement side chains—so many that they cannot fit on the cell surface and are instead secreted into the circulation. According to Ehrlich's theory, these circulating side chains are antibodies, they are tuned and capable of neutralizing a disease-causing toxin. Then they remain in circulation, thereby immunizing the individual against subsequent infestations of the infectious agent. Phagocytosis is the process by which certain living cells, called phagocytes, engulf other cells or particles. Phagocytosis is primarily a

protective reaction against infection and the penetration of foreign substances into the body (Figure 2).

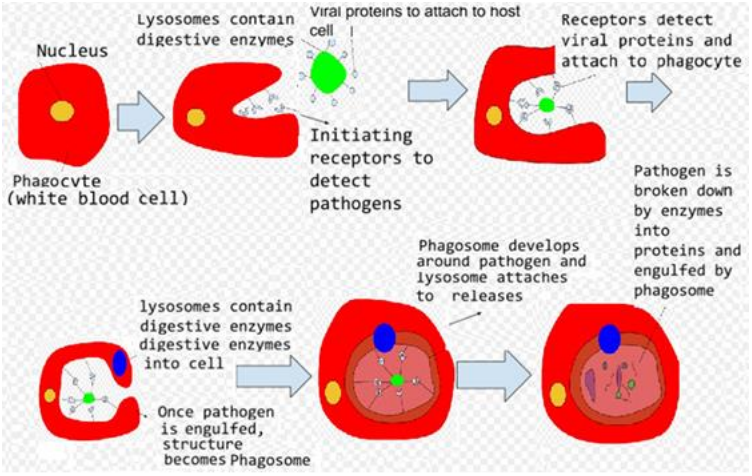

Figure 2. Absorption of the pathogen by phagocyte [2]

3. WHITE BLOOD CELLS - KEY FIGHTERS AGAINST INFECTIONS

White blood cells (leukocytes) are cells of the immune system that participate in the protection of the body both from diseases and foreign invaders (Table). Leukocytes produce hydrogen cyanide during phagocytosis and can kill bacteria, fungi, and other pathogens, producing several other toxic chemicals.

Table. White blood cells overview [3]

Type	%	Main targets
Neutrophil	62%	Bacteria and Fungi
Eosinophil	2.3%	Larger parasites and Modulate allergic inflammatory responses
Basophil	0.4%	Release histamine for inflammatory responses
Lymphocyte	30%	B cells: releases antibodies and assists activation of T cells T cells: • CD4+ T helper cells: activate and regulate T and B cells • CD8+ cytotoxic T cells: virus-infected and tumor cells. • Gamma delta T cells: bridge between innate and adaptive immune responses; phagocytosis • Regulatory T cells: Returns the functioning of the immune system to normal operation after infection; prevents autoimmunity Natural killer cells: virus-infected and tumor cells.
Monocyte	5.3%	Monocytes migrate from the bloodstream to other tissues and differentiate into tissue-resident macrophages.

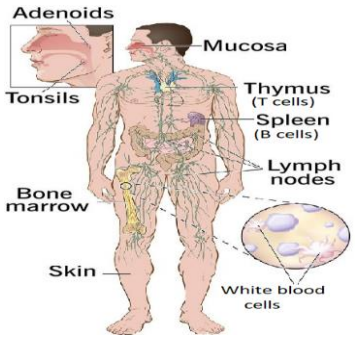

Figure 3. Immune system and lymphocyte sources

The thymus is a specialized primary lymphoid organ of the immune system (Figure 3). T cells born in the bone marrow migrate to the thymus to develop (or mature). After migrating to the thymus, progenitor cells mature into several different types of T cells. T cells are critical to the adaptive immune system, where the body adapts to specific foreign invaders. T cells can be distinguished from other lymphocytes by the presence of the T cell receptor (TCR) on their cell surface.

B cells (B lymphocytes) function in the humoral component of immunity of the adaptive immune system. B cell activation occurs in secondary lymphoid organs such as the spleen and lymph nodes. After B cells mature in the bone marrow, they migrate through the blood to the spleen, which receives a constant supply of antigens through circulating lymph.

B cells produce antibody molecules that can either be secreted or inserted into the plasma membrane, where they serve as part of the B cell receptors (BCRs). When a naïve or memory B cell is activated by an antigen, it proliferates and differentiates into an antibody-secreting effector cell known as a plasmablast or plasma cell. In addition, B cells present antigens (these B cells are called antigen-presenting cells, APCs), as well as secrete signaling proteins known as cytokines (Figure 4).

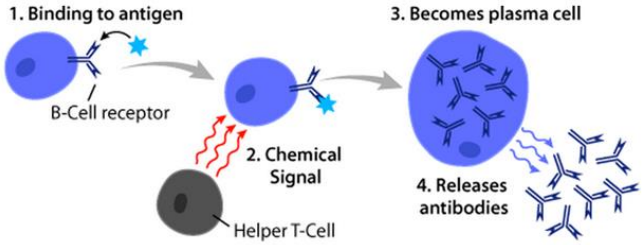

Figure 4. The main functions of B cells are (1) to bind to antigens, (2) to receive help from a related T helper cell, (3) to differentiate into a plasma cell that (4) secretes antibodies

Regulatory T cells are a special population of T cells that provide a critical tolerance mechanism by which immune cells can distinguish invading cells from self. This prevents immune cells from reacting inappropriately against their own cells, known as an “autoimmune” response. Unfortunately, these same regulatory T cells can also be used by cancer cells to prevent tumor cells from recognizing and mounting an immune response against them. This is one difficult and unclear question.

4. DENDRITIC CELLS – NATURE'S MIRACLE

Dendritic cells (DCs) are white blood cells that can carry on the task of antigen-presenting cells (a critical danger detection function) by monitoring human tissue. Dendritic cells (DCs) are professional antigen-presenting cells that participate in the fight against invasive pathogens while promoting tolerance to self- and harmless environmental antigens. They capture pathogens and receive signals from pathogens that influence immune responses. Once activated, they migrate to the lymph nodes, where they interact with T cells and B cells, initiating and shaping the adaptive immune response [4]. They act as intermediaries between the innate and adaptive immune systems.

Different pathogens trigger different maturation profiles of dendritic cells, resulting in a polarization of different T cell subsets. Thus, the adaptive immune response is modulated to some extent according to the nature of the pathogen. An antigen-presenting cell (APC) is a cell that displays antigen bound by major histocompatibility complex (MHC) proteins on its surface; this process is known as antigen presentation. T cells can recognize MHC complexes using their T cell receptors (TCRs). APCs process antigens and present them to T cells (Figure 5).

Migration of DCs from peripheral tissues to lymphoid organs is key to their antigen transport functions. Upon microbial contact with inflammatory cytokines, resident DCs move from non-lymphoid tissues to the lymph nodes' T-cell regions and initiate immune responses [5]. Antigen-presenting cells are key to an effective adaptive immune response, both cytotoxic and helper T cells are dependent on APCs for function. For discovering the central role of dendritic cells in the adaptive immune response, Ralph Steinman (1943–September 30, 2011), a Canadian-American physician, was awarded the Nobel Prize in Physiology or Medicine in 2011. (However, the committee was not aware that he had died three days earlier, on September 30.)

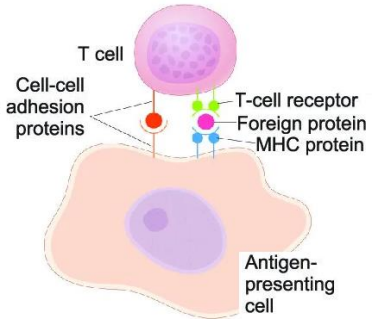

Figure 5. How APCs work [5]

The exact genesis of dendritic cells and their interrelationship is only marginally understood at the moment, in recent years they have become the subject of deep research [6].

5. ON IMMUNE SYSTE MODELMS IN SHORT

There are currently two predominant models of the immune system: Self/Nonself and Danger Theory. The danger model theory of how the immune system works was proposed by Polly Matzinger (born 1947), a French-born immunologist, in 1994. We follow here the very popular Matzinger's paper [7] (cited 5929 times) and use the figures from [8] to illustrate the evolution of IS theories.

The Self/Nonself model. The key proposal here is that the differentiation of self and non-self determines the primary mechanism of this immuno-pathway. The Model was developed by Australian virologist Macfarlane Burnet (1899 –1985) in 1959 [9]. His hypothesis is the following (Figure 6a):

(i) Each lymphocyte expresses multiple copies of a single surface receptor specific for a foreign entity
(ii) Signaling through this surface antibody initiates the immune response
(iii) The self-reactive lymphocytes are deleted early in life.

This strong model gained general acceptance [10], and in 1960, Burnet and Medawar shared the Nobel Prize for their work, and the SNS discrimination model has some extent dominated nowadays.

The first Modified SNS Model. Some new findings in immunology were coming soon, the original SNS model has changed. The first modification happened in 1969 after the discovery that activated B lymphocytes can create new, potentially self-reactive cells. Bretscher and Cohn [11] added a new cell (the helper T cell) and a new signal (help). They proposed that the B cell would die if it recognized the antigen in the absence of help (Figure 6b).

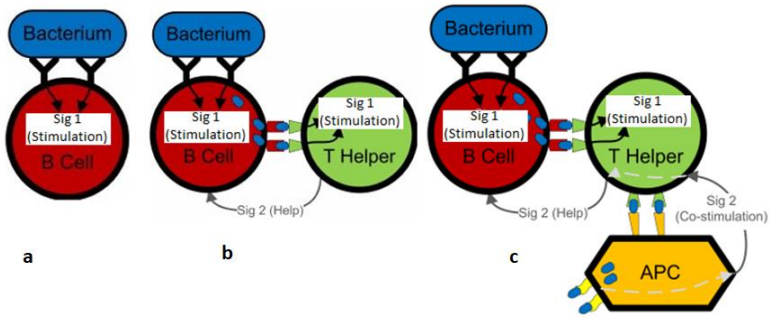

Figure 6. Self/Non-self Model: (a) B cells are activated by the recognition of foreign things (1959); (b) 1st modification (1969): B cells die when they see antigen (signal 1) unless rescued by help (signal 2); (c) 2nd modification (1975): T helper cells die when they see antigen unless rescued by co-stimulation (signal 2) from APCs

2nd Modified SNS Model. In 1975, Lafferty and Cunningham [12] pointed out that T cells respond more strongly against foreign cells of their species than against cells of another species. To account for this effect, they added one more cell and one more signal. Their proposal – T cells need a second signal (named "costimulation"), which they receive from "stimulator" cells (called antigen-presenting cells, APCs). They suggested that this signal is species-specific (Figure 6c). This model solved one problem of species specificity but reintroduced the additional problem of self-reactivity since APC cells express both self and non-self cells meaning possibly stimulating an autoimmune response.

The Infectious-Nonself (INS) Model. The need for costimulation, as Lafferty and Cunningham assumed, complicated the SNS model and posed a new key problem. If the decision to respond is made by antigen-specific cells, and if self-reactive ones are deleted, then immunity can be directed against nonself. In 1989, Charles Janeway Jr (1943-2003) offered an original solution [13] (this paper cited 4552 times), suggesting that APCs can recognize evolutionarily distant pathogens. He proposed a very important point relating to APCs. He proposed that APCs are quiescent until they are activated via a set of pattern recognition receptors (PRRs). For this, Janeway considers two additional molecular patterns: these PRR receptors recognize conserved

pathogen-associated molecular patterns (PAMPs) released by damaged cells (Damage-Associated Molecular Patterns, DAMPs). After activation, APCs up-regulate costimulatory signals, process the bacterial antigens, and present them to passing T cells (Figure 7). Later he developed an INS model [14] that the PRRs allow APCs to discriminate between "infectious-nonself" and "noninfectious-self".

Unfortunately, Janeway's infectious nonself (INS) model by solving old problems created new complexities. How to explain why viruses stimulate immunity, why transplants are rejected, what induces autoimmunity, why tumors are sometimes spontaneously rejected, etc? Over the years, Janeway's model has been modified in its final view [15] but still has difficulty making clear some of these fundamental processes.

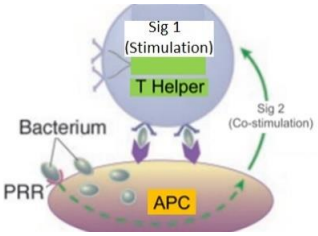

Figure 7. INS model (1989): APCs do not co-stimulate unless activated via PRRs

6. THE DANGER MODEL

30 years by now, in 1994, Polly Matzinger formulated the Danger model [16] (this fantasy-based paper cited 6590 times). She theorizes that the immune system identifies threats to initiate an immune response based on the presence of pathogens and/or alarm signals from stressed cells. She proposed that the immune system is less concerned with the origin of antigens (self or non-self) than with their interaction with our body (tissue damage vs. tissue homeostasis).

The Danger model added a new cellular and signaling layer to the understanding of the immune system [16], suggesting that APCs are activated by danger/alarm signals from injured cells, such as those exposed to pathogens, toxins, mechanical damage, etc. (Figure 8). Cells that die through normal programmed processes are usually cleared before they divide. In contrast, cells that die involuntarily shed their contents. Any intracellular product released can be a danger signal. An important feature is that danger/alarm signals must not be sent by healthy cells or cells undergoing normal physiological death.

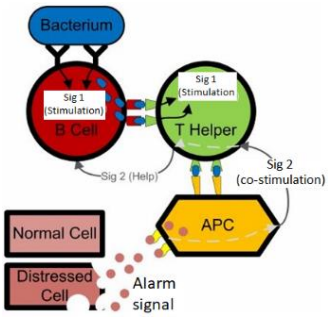

Figure 8. Danger Model diagram (1994) words of: APCs are activated by alarm signals (as firemen in the Matzinger)

The danger model is broad, covering topics as diverse as transplantation, maternal/fetal immunity, autoimmunity, cancer treatments, and vaccines. Matzinger argues that prior models failed to explain why immune system responses vary based on the specific threat's location and severity [17]. The Danger model describes the immune system as a constantly working mechanism that closely monitors and supervises the molecular composition of our tissues and thus tolerates age, gender, and other changes that occur or develop over a lifetime. In other words, the "army" (immune cells) is "politically" controlled by those that it protects, namely, the "environment and inhabitants" (somatic tissues).

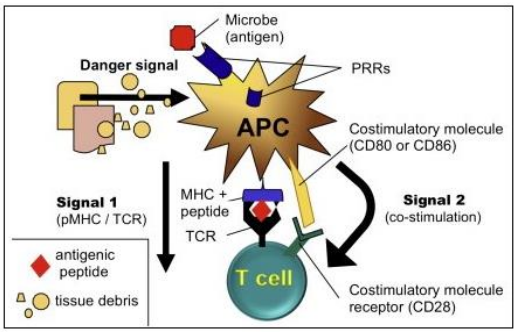

Figure 9. The Danger model in detail [18]

The danger theory has added to the signal described above (self/non-self discrimination) other signals from the microenvironment that cause alarm through antigen-presenting cells (danger, compromised integrity, or disappearance of a conserved tissue form). In detail, the "Danger" model describes either an exogenous or an endogenous (to the body) dangerous alarm that activates APCs, with which T cells, in turn, activate an immune response. The essence of the alarm is threefold: death (necrotic), suffering, and damage (Figure 9). This is different from the PRR model where the APC sends an alarm. Here in the Danger model, APC gets. Danger-associated molecular patterns (DAMPs) have been proposed to represent intrinsic cellular stress molecules leaked from cells and picked up by various receptors. Thus, Danger theory predicts the equality of endogenous or exogenous stress signals in the activation (maturation) of dendritic cells (which can activate T cells).

The differences between the main immunological models. Let us summarize the evolution of the main models that are characteristic of their [7]. Although the SNS, INS, and Danger models share some features, an analysis of their underlying assumptions shows that they are fundamentally different. Is it a microorganism nonself or is it dangerous? Since nonself is sometimes dangerous, the definitions overlap but are not identical (Figure 10):

- For dangerous non-native pathogens (clusters d and e) or harmless themselves (cluster a), both models make the same predictions.
- However, some things (clusters b and f) are alien but harmless (e.g. fetuses),
- while others (cluster c) are themselves but harmful (e.g. some mutations).

For these entities outside the overlap clusters, the INS and Danger models make differences:

- SNS models divide all antigens into two clusters: self and nonself (clusters a and b).
- The INS model divides antigens into "non-infectious self" (cluster a) and "infectious non-self" (cluster f), suggesting the existence of pathogen-associated molecular patterns (PAMPs) evolutionarily conserved on pathogens that are very distant from their hosts,

and that host APCs may therefore have pattern recognition receptors (PRRs) to detect them. It tends to ignore clusters b and f.

- The danger model divides antigens into those associated with dangerous or harmless entities, defining as dangerous anything that causes stress or non-physiological cell death. Dangerous entities can be themselves (cluster c), such as mutations that cause stress cell death, or inefficient clearance; or non-self, such as pathogens (cluster e), environmental toxins (cluster d), and the like. Cluster f would include evolutionarily distant organisms that have PAMPs but are not dangerous.

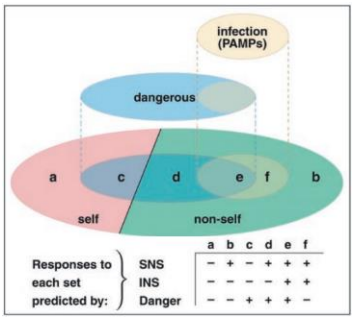

Figure 10. Partitioning the universe of antigens: three IS models [7]

Tumors are objects for which both the INS and danger models have the same predictions, namely that tumors should not stimulate immunity, either because they (in INS) are not associated with microbial stimulators, or because they (Danger) are healthy growing cells that do not send alarms.

Thus, to eradicate a tumor, we should:

- infect it,
- or create repeated lesions to alert local APCs,
- or we should revaccinate with an immune-stimulating tumor vaccine.

Cell death model. Cell death is another tough problem [19]. Cell death products, collectively known as DAMPs (Damage-Associated Molecular Patterns), form a feedback loop that stimulates Pattern Recognition Receptors (PRRs) to trigger inflammatory/immune responses. The proteins PPRs capable of recognizing molecules frequently associated with pathogens (Pathogen-Associated Molecular Patterns, PAMPs), or molecules released by damaged cells. They are considered part of the innate immune system. Molecularly controlled forms of cell death are part of a very ancestral mechanism involved in key aspects of the physiology of multicellular organisms to eliminate unwanted, damaged, or infected cells. The engagement of PRRs in response to PAMPs induces the activation of different cell death types of machinery to promote tissue homeostasis and host defense against pathogens. Importantly, cell death products (DAMPs) form a feedback loop that stimulates PRRs to induce inflammatory/immune responses

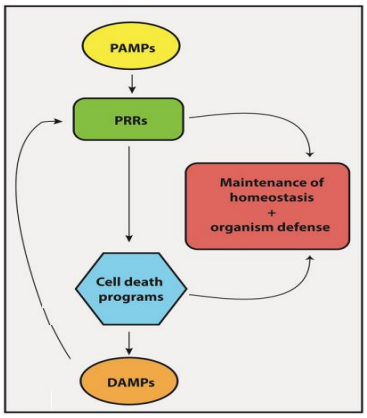

Figure 11. Interaction between PRRs and cell death mechanisms

As a comparison of the three basic IS models (Figure 10) shows, there is a huge amount of work ahead, e.g. transplantation, maternal/fetal immunity, autoimmunity, many unclear cancer treatment aspects, and much more.

7. AN INSIGHT INTO MATHEMATICAL MODELING

Let's consider just a few of the simplest models based on ordinary differential equations.
Lotka-Volterra Predator-Prey Model (1920). This is a popular model [20]. It assumes that 1) the population of prey (hares) grows exponentially in the absence of predators (wolves), 2) each wolf kills a certain fraction of the hare population per unit time, 3) the birth rate of wolves increases linearly with the rate of consumption of hares, and 4) wolves are constant death rate. This model has a neutrally stable equilibrium between prey and predator population sizes. This means that at any initial starting point, the prey and predator population sizes are constantly fluctuating. The magnitude of these fluctuations increases with the distance of the initial conditions from the equilibrium point $x^* = c/d$, $y^* = a/b$.

The original model had four terms as follows:

$$x' = ax - bxy$$
$$y' = -cy + d(bxy)$$

where x is the population size of the hare and y is the population size of the volf, a is the per capita birth rate of the hare, b is the encounter probability between volf and hare (bx is the rate at which a volf individual kills hare), c is the per capita death rate of the volf, and d is the conversion efficiency of hare consumed by a volf into new volfs.

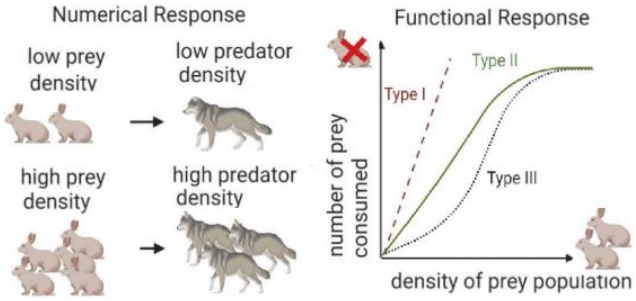

Figure 12. Predator-Prey Model: numerical vs functional response

The numerical response (Figure 12) describes the conversion of hare density into volf density, and the functional response captures the relationship between the rate of consumption and food density. Type 1 shows the case that the rate of consumption of volfs is proportional to hare density. Type II relates to the case that the number of hares consumed increases rapidly with increased hare population density but plateaus at a carrying capacity. Type III is similar to Type II but assumes that at low hare density rate of hare consumption is slower than in Type II.

Cancer model. The Lotka-Volterra model is useful for the description of the competition between two distinct cancer cell populations [21], between drug-sensitive (S) and drug-resistant (R) cells (Figure 13), describing in a form of the following equations:

$$\frac{dS}{dt} = r_S\left(1 - \frac{S+R}{K}\right)S - \delta S$$

$$\frac{dR}{dt} = r_R\left(1 - \frac{C*S+R}{K}\right)R$$

where r_S and r_R indicate the intrinsic growth rates of S and R, respectively. The term $\delta > 0$ imposes a death rate on S due to therapy.

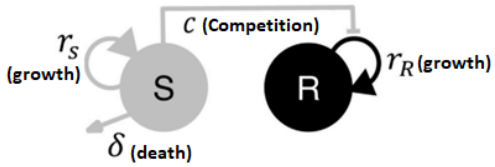

Figure 13. The mathematical model of tumor growth and treatment

Oncolytic virotherapy model [22]. Viruses are infectious agents that depend on a living host cell for replication. Oncolytic agents primarily move in tumor cells, leading to tumor cell lysis and severe antitumor effects, such as innate and adaptive immune responses and destruction of tumor vasculature. Infectious disease modeling has a long-life history in mathematics to represent the spread and cytotoxic effects of viruses.

Oncolytic virotherapy model is the following: host cells are divided into susceptible (uninfected, S) and infected (I) cells, where the total number of tumor cells is $C = S + I$ and viral population V. The term $\beta_I I$ is described as directly affecting the number of virus particles (δ). The term for viral infection is γVS, and the term $u_V(t)$ simulates the effect of oncolytic virotherapy, and virus particles administered at time t (Figure 14).

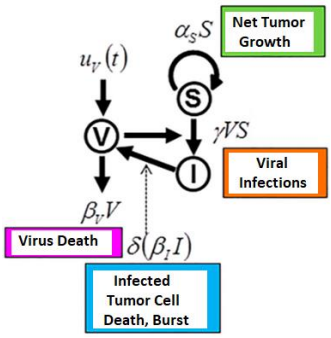

Figure 14. Oncolytic virotherapy model

Thus, we get the following equations:

$$\frac{dS}{dt} = \alpha_S S - \gamma VS$$
$$\frac{dI}{dt} = \gamma VS - \beta_I I$$
$$\frac{dV}{dt} = u_V(t) + \delta(\beta_I I) - \beta_V V$$

Birth–death process of phagocytosis. In [23], the well-known process of birth and death (a simple Markov model) is expanded for the modeling of phagocytosis. The model considers stochastic interactions between bacteria and immune cells as well as heterogeneity in the susceptibility of individual hosts to infection within a population. The dose-time response to intracellular bacterial infection dynamics after inhalation can be described by the birth-death process.

We have the following state definition $\{T, P\}$ where T is the total number of extracellular bacteria, and P is bacteria-containing phagocytes. The birth, death, and survival rates are $\lambda > 0$ and $\mu > 0$ and $\alpha > 0$ respectively and the threshold for illness is M (Figure 15).

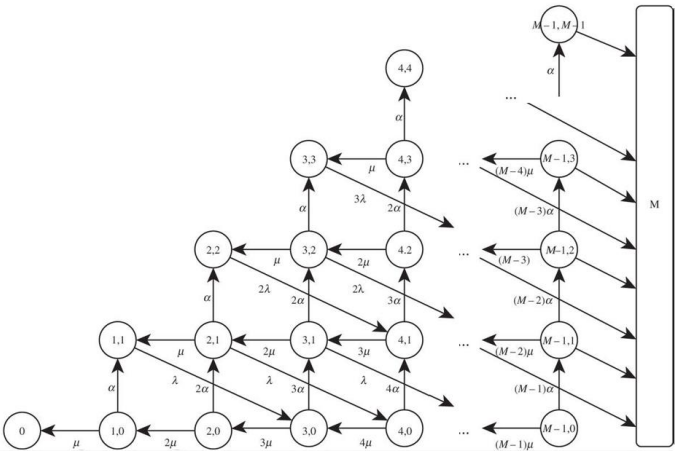

Figure 15. The Markov chain of the birth-death-survival process

The Kolmogorov equations (in the form of ordinary differential equations) are the primary means to solve a time-homogeneous Markov process.

8. FUTURE WORK

Melanoma case. We will demonstrate the complexity of the problem using the example of the fight against melanoma [24], keeping in mind the mathematical model of melanoma. Melanomas are among the most immunogenic tumors and therefore have special attention to immunotherapy. We look at two parts: innate immunity and adaptive immunity (Figure 16).
Innate immunity. Several therapeutic strategies to inhibit melanoma growth specifically target the activation of antitumor activities in innate subsets found in tumors:

- Natural killer (NK) cells bind tumor cells through receptor/ligand interactions and release cytolytic molecules, causing tumor cell death.

- Phagocytes (such as polymorphonuclear neutrophils, PMNs), macrophages (Mφ), and dendritic cells (DCs) process dead tumor cells and present tumor-associated antigens (TAAs).

- DCs actively use cytokines released from activated NK cells.

Adaptive immunity. Long-term memory responses essential for melanoma remission include the activation and proliferation of adaptive immune cells, namely helper CD4+ T cells and cytotoxic CD8+ T cells. As mentioned above, DCs and to some extent macrophages are most capable of activating adaptive immunity to induce cytotoxicity of CD8+ effector T cells as well as promote the formation of memory immune populations involved in long-term remission. The recruitment of T- and B-lymphocytes by chemokines and the presentation of TAA molecules activate the adaptive part of immunity:

- Tumor-specific CD8+ T-cells bind tumor cells displaying TAAs on MHC molecules through the engagement of the T-cell receptor, which triggers the release of cytotoxic granules by the tumor cells.

- Tumor-specific CD4 + T-cells engage B-lymphocytes using TAAs presented by MHC molecules, leading to the release of TAA-specific antibodies. It causes tumor cell death through various mechanisms.

- Adaptive immune cells also reactivate innate immunity and kill tumor cells, this additionally releases TAA, which is processed by APCs.

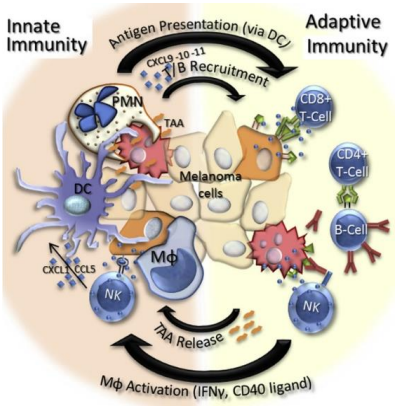

Figure 16. Against Melanoma by Immune Cells [24]

In building the melanoma mathematical model, one needs to consider at least 20 variables and 20 equations respectively (Figure 16). But… the latest cancer research disclosed several unpleasant effects.

On the dual role of macrophages. Numerous experimental studies have documented dual – anti-tumor and pro-tumor – roles of Th1/Th2 immune cells and M1/M2 macrophages. It relates to melanoma to a great extent. However, it is still unknown how these immune cells interact with each other to control tumor dynamics.

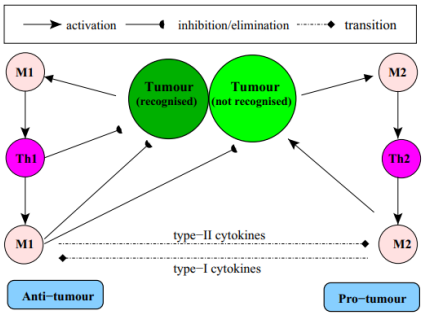

Figure 17. Schematic description of possible tumor-immune interactions

Figure 17 is one basic scheme for a mathematical model representing the interactions between melanoma cells, Th2/Th1 cells, and M2/M1 macrophages, to investigate the unknown role of the re-polarisation between M1 and M2 macrophages on tumor growth [25].
Infiltration of macrophages in and around the tumor nest represents one of the most crucial hallmarks during tumor progression. Macrophages consist of at least two subgroups, M1 and M2:

- M1 phenotype macrophages are tumor-resistant due to intrinsic phagocytosis and enhanced antitumor inflammatory reactions.

- Contrastingly, macrophages M2 have tumor-promoting capabilities involving immuno-suppression.

In [26], mechanisms underlying the distinct functional characterization of M1 and M2 macrophages are demonstrated to make sense of M1 and M2 as key regulators during cancer progression. However, how these immune cells interact with each other to control tumor dynamics remains unknown.

9. CYBER SECURITY ISSUES AND IMMUNOLOGY

Biologically inspired computing is a new area of computer science research that aims to create systems modeled after biological phenomena, which could improve the use of computers [27].

Biologically inspired computing is based on:

(1) genetic algorithms and some knowledge of evolutionary processes,

(2) artificial intelligence (AI) and artificial neural networks (ANN),

(3) sensor networks (which model sensory organs), or artificial immune systems.

The newest area of research is cyberimmunity, which is based on the human adaptive immune system. Artificial immune systems (AIS) are looking for the parallels between the functionalities of intrusion detection systems and biological immune systems [27]. AIS computational methods draw inspiration from biological immunity, to learn and adopt some principles selected by evolution. A key feature of intrusion detection systems based on AIS algorithms is their proficiency distinguishing “self” from “non-self” cells. These algorithms include (1) the negative selection algorithm, (2) the positive selection algorithm, and (3) the clonal selection algorithm. These AIS algorithms share similarities with neural networks, as they incorporate system training based on a specified dataset.

Summing up, it is worth considering the cyber threat problem from two sides.

On one side, there are still many uncertainties in the human immune system and much to be studied but without of doubt, this new approach may initiate many new ideas.

On the other, it is reasonable to turn attention to real life representing many failures in the fight against cyber threats. Let us recall only a single example from the experience of the U.S. Army Cyber Command. Command was set up in 2010 and its many painful failures should be studied, particularly with Joint Regional Security Stacks (JRSSs), which illustrate the complexity of combating cyber threats. The JRSS network mission was to continuously monitor and analyze the military information networks for increased situational awareness and minimize the effects of cyber threats while ensuring the integrity, availability, confidentiality, and non-repudiation of data. Unfortunately, in 2021, the Pentagon suspended this $2 billion cybersecurity project because JRSSs were too slow and didn't meet bandwidth requirements [28]. Now artificial intelligence is a great hope. Could it be more successful?

Looking for parallels between human and artificial immune systems may offer probably some revolutionary solutions.

10. CONCLUSIONS

The article has two goals: to attract the interest of mathematicians to immunology and to look for ideas for Cyber Defense Systems considering the human immune system as a highly sophisticated defense system against any dangers.

Looking to the sunrise of immunology Ilya Mechnikov (1845-1916) and Paul Ehrlich (1854-1915) are mentioned.

White blood cells (leukocytes) are cells of the immune system that participate in the protection of the body both from diseases and foreign invaders.

The differences between the three main immunological models (Self/Non-self Model, Infectious-Nonself Model, and Danger model) are considered.

A few of the simplest models based on ordinary differential equations are given in short.
Melanomas are among the most immunogenic tumors and therefore have special attention to immunotherapy. In this context, the dual role of macrophages is mentioned.

The newest area of research is cyberimmunity, which is based on the human adaptive immune system. Artificial immune systems (AIS) are looking for the parallels between the functionalities of intrusion detection systems and biological immune systems There are many unsolved issues. Only a single example from the experience of the U.S. Army Cyber Command is recalled. It relates to Joint Regional Security Stacks (JRSS). Unfortunately, in 2021, the Pentagon suspended this $2 billion cybersecurity project because JRSSs were too slow and didn't meet bandwidth requirements. Now artificial intelligence is a great hope.

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