Unique Properties of the Immune System

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The human body is unquestionably one of the most complex systems known to humanity. There are three main regulation systems in the human body (the nervous system, the endocrine system and the immune system). These three systems are integrated into one ultimate information communication network within the human body. However, each regulation system has its specific roles and unique properties. Consequently, each of these regulation systems has served as inspiration for computational models to efficiently solve real-world problems. An overview of these models and their applications is presented.

nervous system | immune system | endocrine system | artificial immune system | computational models

1. Nervous, Endocrine-, and Immune System

The nervous system is a highly ramified network with a hierarchical order controlled by a central controller (the brain). Information is transported via electrical impulses that can be amplified or blocked by messengers. The nervous system, and particularly, the brain have been used as inspiration for computer scientists for a long time (e.g., in artificial neural networks (ANNs)).

On the other hand, the endocrine system is a regulation system purely based on chemical messengers (i.e., hormones; cf. [1]). These chemical messengers are secreted by different source organs (called glands) in the human body. The regulation itself happens with specific feedback loops of the hormones as almost every hormone has a complementary hormone [2]. The endocrine system tries to establish homeostasis (or feedback inhibition) between the chemical messengers by regulating the secretion of the respective complementary hormones. The endocrine system has some interesting properties [3], such as self-organization, synchronization, and cascading effects, that offer inspiration for certain computational problems.

In [3], Sinha and Chaczko compared the basic structure and working principle of the endocrine system with large-scale Internet of Things (IoT) infrastructures. Based on this view, they argue that models derived from the endocrine system offer great potential to solve problems prevalent in such large-scale networks. For this reason, several computational models based on the endocrine system have been proposed in the past, such as the autonomous decentralized system [4][5][6], the digital hormone system used for self-organized robot swarms [7][8][9],

the computational model of hormones as first proposed in [10] and extended in [11], the regulation model of hormones [12][13], as well as the artificial hormone system [14][15].

The third regulation system, the immune system, is a widely distributed and inherently parallel network of a significant number of diverse entities. These entities work simultaneously and in cooperation with each other to reach the overall goal, to keep the body healthy [16][17]. It is a decentralized system without a central controlling instance (such as the brain for the nervous system). One of the most significant advantages of the HIS is its vast amount of resources. The immune system of an adult consists of around 10121012 lymphocytes, 10201020 soluble antibody molecules with about 5 million different antibody types, and a daily turn-over of these components of approximately 2% (cf. [18]).

Additionally, the HIS operates on different levels using various components, such as physical barriers (e.g., skin), chemical barriers (e.g., antimicrobial substances such as sweat and saliva), cellular proteins (e.g., cytokines), and a large number of different cells (e.g., macrophages and DCs). All these components and their interactions build up a highly complex self-organizing system with beneficial properties, such as error tolerance, adaptation, and self-monitoring [19]. Certain parts of the immune system even have learning, memory, and associative capabilities (cf. [20]).

2. Innate and Adaptive Immunity

The immune system has an ingenious multi-layer defense mechanism consisting of two distinct yet interrelated immune mechanisms [21]:

- Innate (non-specific) immunity.
- Adaptive (specific) immunity.

The combination and interaction of both form versatile and efficient protection for the human body. Both parts of the immune system use many different cells of diverse specialization to protect the host efficiently.

2.2.1. Innate Immunity

The innate immune system [22] provides non-specific protection and defense mechanisms, as well as general immune responses. There are four types of defense barriers in innate immunity, namely (cf. [21]):

- Anatomic barriers;
- Physiologic barriers;
- Endocytic and phagocytic barriers;

- Inflammatory barriers.

Innate immunity consists of a large number of different cells providing a defense against the general properties of pathogens [23]. Hereby, the APCs (a kind of leukocyte, or more specifically monocyte) play an important role, especially the DCs (see Section 4.3). The innate immune system is an essential first line of defense against invading pathogens using generic responses [24]. The innate immune system does not develop memory and, thus, does not offer specific responses [25]. A review of innate immunity and its biological principles and properties can be found in [26].

2.2.2. Adaptive Immunity

The adaptive immune system [27] provides more specific and compelling response mechanisms, as well as the capability to learn from previous occurrences of pathogens (i.e., immune memory [28]). It is sometimes called *acquired immunity* as the specific responses are developed over the lifetime of the host [19]. The main components of the adaptive immune system are lymphocytes, in particular B and T cells. In contrast to the leukocytes constituting the innate immunity, these cells can evolve over the lifetime of the host by specializing their receptors [29]. Based on these cells and their contribution to adaptive immunity, two primary adaptive immune responses can be distinguished, the *humoral response* and the *cellular response* [25][30][31].

The *humoral response*, or humoral immunity, refers to the interaction of B cells with antigens by producing specific antibodies that detect and eliminate foreign entities. B cells are produced by the bone marrow, where they have to survive a negative selection process before being released into the bloodstream. This negative selection process is part of the SNS theory and makes sure that the B cells surviving are self-tolerant; thus, they do not attack native (self) cells. If a B cell matches a particular antigen, it responds by multiplying itself through clonal expansion. In this process, B cells divide into several clones with slightly mutated antibodies to cover a broader spectrum of antigens and increase the chance of an even better antigen matching [32]. B cells with a high affinity can evolve to memory B cells capable of identifying the same pathogen much faster in the future (as the activation and stimulation process is shorter for memory B cells [33]). Such an immune response from memory B cells is called immune memory (also referred to as secondary immune response or strong immunity [28]) and provides an essential characteristic of the adaptive immune system, namely the ability to learn through interaction with the environment. Approximately 90% of the B cells die after their responses or lifespans, and the rest remain as memory cells [34].

The second adaptive immune response is the *cellular response*. It refers to the behavior of T cells that have two main tasks:

- The detection of intrusions by T helper cells (T_h).
- The attraction of cytotoxic T cells (T_c) for the disposal of infected cells [31].

To be more precise, the T_c becomes activated on the recognition of infected cells and starts producing molecules that destroy the infected cell.

In addition to T_h and T_c, there exists a third type of T cells, the regulatory T cells. These regulatory T cells exist in two different stages: naive or active [34]. After being produced in the bone marrow, these regulatory T cells migrate to the thymus where they undergo a negative/positive selection process similar to B cells (but in the thymus instead of the bone marrow). Regulatory T cells that survived the selection process and that have not experienced an antigen yet are called *naive T cells*. Naive T cells can become *activated T cells* if they successfully bind to an antigen in combination with co-stimulation from an APC (or DC to be precise; see immune models in Section 2). Thereby, the degree of activation depends on the degree of signaling from the DC. In the case of excessive levels of co-stimulation, the T cells die to prevent overly excessive immune responses, a process called activation-induced cell death [35].

3. White Blood Cells

Although many cells are involved in immunity, white blood cells build the core of the immune system. These cells are primarily produced and matured in lymphoid organs (e.g., thymus or bone marrow). They are categorized in general white blood cells, *leukocytes*, and specific subtypes of white blood cells, *lymphocytes* [36].

While leukocytes form the basis of innate immunity (i.e., monocytes such as macrophages and APC), the adaptive immune responses are primarily performed by lymphocytes (i.e., T and B cells, as well as natural killer cells) [37]. The three most important white blood cells for immunity are:

- **dendritic cell (DCs)** are a particular class of APCs that moves in blood and processes information about antigens and dead cells found in their way.
- **T cells** are produced by the bone marrow and are responsible for destroying infectious cells.
- **B cells** are also produced by the bone marrow and stimulate the production of antibodies.

Due to their way of detecting foreign antigens, the antibodies are often called detectors, especially in the context of AIS.

In addition to the white blood cells, a large number of other cells and molecules are essential for the functioning of the immune system. Thereby, the ligands (or keys) play an important role as they are responsible for activating the cells' receptors. As with the endocrine system, also the immune system contains regulating molecules called cytokines. Additionally, chemokines are specialized molecules that stimulate cell movement [36].

Altogether, the immune system shows characteristics also found in other bio-inspired systems. As the cells and their interaction share similar properties with swarm-like systems, the immune system is often considered a swarm system, too [38]. Also, to detect foreign entities, the immune system uses affinity measures that are, in their

fundamental principle, similar to the fitness function in genetic algorithm (GA) [30]. A detailed overview of the (natural) immune system can be found in [21][39].

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