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Immunity in Light of Spinoza and Canguilhem

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Abstract: All living organisms are under stress imposed by their surrounding environments. They must adapt to their stressors to live and survive. At the forefront of this adaptation is a defense system called immunity. Immunity, as the most ancient cognitive apparatus with memory function, is present in all living organisms. In previous reports, minimal cognitive function was defined as a “biologized” concept—namely, perception of elements in a milieu, integration of perceived information, reaction according to integrated information, and memory of that experience. In this study, I aim to explore the essential feature of immunity by synthesizing scientific facts and “metaphysicalizing” them with logical reasoning. As a result of my analysis, I have realized the essential element in immunity: the capacity to preserve the existence of organisms by regulating their physiology and pathology. Having further analyzed immunity with special reference to the philosophy of Baruch Spinoza and George Canguilhem, *conatus* (“appetite”, to be precise) with normative activities is deeply embedded in immunity and may constitute its essential feature. Given that *conatus* and normativity imply mental elements, including the judgment of good and bad or health and disease, it is possible to conclude that the essential function of immunity includes cognition with normative connotations. This inclusive view encourages us to rethink the fundamental nature and philosophical implications of immunity from the cognitive perspective.

Keywords: appetite; cognition; *conatus*; immunity; metaphysicalization; normativity

1. Introduction

Humanity has known the phenomenon of immunity for centuries. Thucydides, for example, an Athenian historian, described the phenomena that remind us of immunological memory and specificity during the Peloponnesian War in the 5th century BC [1]. Since then, the problem of immunity has attracted widespread attention, mainly for the practical reason of controlling infectious diseases. At the turn of the 20th century, theoretical considerations and debates about the mechanism of immunity began, and immunology has since undergone a major transformation. As discussed in the next section, we are in a stage wherein we have to change our view of the immune system and immunity.

According to Alain Badiou, a genuine philosopher is someone who invents new problems and intervenes when signs point to the need for new thought. He calls this a “philosophical situation” [2]. Recent developments in the field of immunology, explained in the next section, indicate a need to reformulate the framework of our perspectives on the immune system and to rethink the essential nature of immunity. In previous reports [3,4], I searched for the minimal requirements for the immune system and found that four functional (not structural) components are conserved throughout living organisms—namely, a perception of elements in a milieu, integration of perceived information, reaction according to integrated information, and memory of that experience. The minimal elements constituting immunity are expressed in the bacterial immune system, in the form of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR-associated (Cas) protein [5–12]. I tentatively defined

these four functional elements as an essence of immunity and the CRISPR-Cas system as a prototype of minimal cognition.

The term “cognition” generally designates human conditions associated with higher neural functions, such as abstract thinking and awareness of awareness. However, the definition of “cognition” is controversial, and discussions concerning the nature of cognition have presented a wide spectrum of views, especially regarding the minimum requirements for a process to be recognized as cognitive [13–21]. At one extreme, there is the perspective called “brain-centrism” or “neurocentrism”, which claims that the cognitive process is strictly related to the presence of the brain or brain-related structures, such as neurons, or neuron-associated electrophysiological functions. According to this traditional and commonsensical view, organisms without a brain or neuron-associated structures and functions cannot be cognitive. This view still seems to prevail among mainstream scientists. We have observed severe critiques from those scientists on the domain called “plant neurobiology”, based on the fact that plants do not have neurons [22,23]. At the other end of the spectrum are those who contend that an output involving motor elements is the minimal requirement for cognition [18,24]. One typical example is chemotaxis in bacteria, but biochemical reactions without motor components, such as the *lac operon* system in *Escherichia coli*, are not cognitive [18,24]. However, recently, a more inclusive view has been developed that cognition should include a set of mechanisms in which information acquisition, storage, processing, and use occur at any level of organization, irrespective of the presence of the nervous system [20,21]. The biologized definition of cognition I use in this study is comparable to the last category. With this definition, we can discuss issues common to a wide variety of organisms without considering the subjective world, although it does not solve immediate and concrete human cognition problems.

In this essay, I would like to unveil a new perspective on immunity by incorporating a philosophical process, what I call the “metaphysicalization of science” [4,25,26]. This method is based on metaphysical and logical contemplations of the facts that have been revealed by scientific endeavors. The details will be elaborated in Section 3. In the next section, I commence reflections on recent scientific findings in immunology.

2. Recent Developments of Immunological Thoughts

The theme of the first conflict at the turn of the 20th century concerned what constitutes the fundamental components of immunity [27,28]. One camp, led by Élie Metchnikoff, claimed that the component responsible for immunity is the phagocyte [29], while the other camp, represented by Emil von Behring and Paul Ehrlich, maintained that a serum component in the blood, named *Antikörper* or antibody, is responsible for the defense against infection [30,31]. Initially, the latter idea prevailed but it was later demonstrated that the cellular components play as important a role as that of antibodies. The “side chain” theory of Ehrlich assumed that antibodies, in the form of a side chain on the cell surface, preexist and are released after antigen entry. Although the assumption regarding the selective nature of immune response was correct, Ehrlich thought that one cell expresses a variety of side chains. The observation that the immune system can produce antibodies against an almost unlimited variety of antigens [32] rendered Ehrlich’s theory untenable, because it is physically impossible for a single cell to have so many side chains on the surface.

To overcome this difficulty, the instructive theory was introduced. The principal premise is that antigens play an active role in the process of antibody formation [33,34]. This theory was popular for a period of time, but it could not explain several immunological phenomena, including immunological memory, affinity maturation of antibodies, and the presence of natural antibodies. By the 1960s, the instructive theory was abandoned and the clonal selection theory emerged as a paradigm of immunology [35]. This theory postulates that (1) the entire repertoire of antibodies is present before encounters with antigens, (2) each cell expresses a single type of antibody, (3) antigen binding triggers proliferation of cells, leading to antibody production, and (4) self-reactive cells are eliminated at an early stage of embryonic development.

However, various challenges to this paradigmatic theory have been raised. An incomparable challenge came from Niels Jerne, who tried to understand the immune system in its entirety without reference to the Burnetian distinction between self and nonself. His idiotype network theory was the first of its kind in the conceptualization of the functioning of the immune system [36]. The idiotype signifies the three-dimensional structure of the variable region unique to each immunoglobulin and induces the immune response as an antigen. From this experimental result, Jerne imagines that antibodies bind to one another by idiotype–anti-idiotype interaction, thus forming a global, systemic network in the organism. According to this theory, the immune system is viewed as self-sufficient, self-referential, and closed. The normal state of the immune system is not at rest but is maintained by the dynamic interaction of antibodies, leading to a state of equilibrium. An antigen disrupts this equilibrium at the organismal level. Thus, the teleological significance of antibodies can be explained because all antibodies are supposed to be involved in the maintenance of organismal equilibrium. However, with intensive and extensive work that lasted from 1975 to about 1990, it was impossible to justify his theory with experimental data. Consequently, it is now considered a fictitious concept in immunology and has almost been completely forgotten [37,38].

Irun Cohen also pointed out that the clonal selection theory does not provide a satisfactory explanation for the fact that there are autoreactive lymphocytes and natural autoantibodies in healthy individuals. He recognized the clonal nature of lymphocyte activation but criticized the clonal selection theory's reductionist and mechanistic nature and its lack of a nuanced and global perspective. In the 1990s, he offered an alternative by proposing a cognitive paradigm based on the assumption that the immune system is an information-handling system comparable to the central nervous system [39–41]. The central nervous system extracts information and uses previously deposited information or experience to transform it into an effective means to deal with the external world. The clonal selection theory states that lymphocytes are passively selected by antigens, but the cognitive paradigm, in contrast, posits that the immune system must know how to focus on an antigen and how to evaluate the context of interaction. In a way, Cohen sees a sense of direction or a kind of intentionality, but not consciousness in lymphocytes or in the immune system [41].

Subsequent challenges concerning what triggers the initial activation of immune responses were made by Janeway's theory of discrimination between the infectious nonself and the noninfectious self [42,43] and by Matzinger's danger theory [44]. Janeway's theory assumes that the innate arm of the immune system—specifically antigen-presenting cells—has to be activated before lymphocyte activation, and that the initial interaction takes place between the pattern-recognition receptors on the antigen-presenting cells and the microbe-associated molecular patterns of microorganisms. Thus, this proposal implies that evolution and activation of the immune system are dependent on the presence of microorganisms. However, several problems have been highlighted, particularly by Matzinger: for example, why does an allograft free of microorganisms induce rejection responses, and what causes autoimmune diseases? She developed the thesis that the signal initiator of the immune response does not necessarily comprise microorganisms or the nonself but includes all the internal changes that are potentially dangerous to the host. In other words, endogenous changes generating a danger signal can activate the immune system. These proposals are significant contributions to the understanding of the fundamental workings of the immune system.

The problem of self and nonself has been discussed since the early days of the clonal selection theory [45–48]. Recently, based on another criticism of the notion of self and nonself, the requirement for what triggers immune responses was defined [49]. According to this proposal, the immune system is activated only when it senses the breaking of the spatiotemporal continuity in the body by reacting with the antigenic difference, which is not necessarily the one between self and nonself. The essential factors that influence the onset of the immune response are characterized as follows: (1) the quantity of antigens, (2) the degree of molecular difference between new antigens and usually encountered antigens, and (3) the speed of the appearance of unusual antigens. More recently, this was refined as the discontinuity theory [50]. According to this version, immunogenicity depends on the mode

of presentation of antigens to the immune system but not on the physicochemical nature of antigens, such that one cannot predict whether or not an immune response will occur solely on the basis of the nature of antigens. Thus, the theory focuses on the same phase that the danger theory tried to explicate. All proposals listed above, except for the idiom network theory, are not negations of the clonal selection theory—specifically the clonal nature of immune responses—but its modifications.

Given recent advances in the field of immunology, we are entering a new phase in which the older conception of immunity as a defense mechanism against microorganisms needs to be modified or be replaced by a new perspective. First, functional interactions in an organism are observed between the immune system and other systems—notably, the nervous system and the endocrine system—such that cells or humoral factors derived from the immune system contribute to the functioning of other systems, and vice versa [51,52]. More significantly, such examples have accumulated with time [53–59]. Recent major additions to this list include gut microbiota that not only control the induction, education, and function of the host immune system but also affect neurological, psychological, and metabolic conditions, possibly through neural, hormonal, and immunological networks [60–65]. The presence of microbiota also stimulates discussions regarding the problems of individuality and organism [66–70].

Furthermore, the classical demarcation between innate immunity and acquired immunity in an organism is less clear today. Immunological specificity and memory, once conceived as the principal and exclusive characteristics of acquired immunity, are seen not only in cells responsible for innate immunity of highly evolved organisms, such as natural killer cells or innate lymphoid cells, but also in organisms previously thought to lack acquired immunity, such as plants, invertebrates, and bacteria [71–76]. These findings suggest that the immune system is not isolated or autonomous but intricately integrated into the structure and the function of a whole organism. As mentioned above, the immune system serves not only as a defense mechanism against external and internal events that cause organismal disturbances but also as a control mechanism of neurological, psychological, and metabolic conditions. Given that an immune system exists in all living organisms, from bacteria to human beings, although the structure and the mechanism are not necessarily the same [74], it is clear that immunity is a fundamental element for all living organisms.

3. What is the Metaphysicalization of Science?

Before going into the search for the essential nature of immunity, I ask why metaphysicalization of science is needed for our purpose. The idea came to me in 2008, when I first read the “Law of Three Stages” in the *Course of Positive Philosophy* of Auguste Comte [77]. It was the second year after my entry into philosophy from science. In his *Course*, Comte posited that the human mind, either as a species or as an individual, successively passes through three different stages: the theological or fictitious, the metaphysical or abstract, and the positive or scientific. Comte first conceived this idea in the *Plan of the Scientific Work Necessary for the Reorganization of Society* [78] and then promoted it to “law” in *Philosophical Considerations on the Sciences and Scientists* [79]. This concept has become the basis for further philosophical meditations. The first theological stage, provisional and preparatory, is based on supernatural or religious explanations of the phenomena. The second metaphysical stage is a modification of the first in that supernatural agents employed to explain the natural phenomena are replaced by abstract entities produced by man. This stage is merely transitional, gradually reaching the third and final stage in which rational and logical thoughts and real observations are adopted as the basis of knowledge, thus abandoning pure imagination. This final stage constitutes the most evolved human reason [77].

The philosophy of Comte was further elaborated and refined by, for example, Ernst Mach and members of the Vienna Circle in the early 20th century, and it was adopted as the guiding principle of science thereafter. As a result, the separation of science from philosophy became decisive. Current scientific activities exclude philosophy and the search for the essence of a thing or a phenomenon. When the social condition is unstable, as it was in the French Revolution, it is natural to seek the reasonable solutions for the stabilization of society by removing fictitious and abstract factors from

people's thinking. That was exactly what Comte experienced. However, for someone who had worked in the field of modern science for a significant period of time, it seemed regrettable to abandon the ways of thinking operating in the first two stages. If the task of metaphysics is to provide a reasonable explanation of nature at its most comprehensive and broadest levels, then a metaphysical analysis should provide us with a richer and fuller understanding of nature. Based on the same rationale, the search for essence will necessarily involve philosophical and metaphysical contemplations of what science has revealed. Thus, I propose implementing the metaphysicalization of science as a way to reach a fuller understanding of nature's realities [4,25,26].

Once science has unveiled the hidden aspects of nature previously discussed in philosophical and metaphysical realms, it is common to replace old philosophical concepts with newly established scientific ones. This revised understanding is what scientific progress signifies. Therefore, it may be paradoxical to bring up notions with philosophical connotations or discuss scientifically explainable phenomena from philosophical and metaphysical perspectives. Nevertheless, the approach used here is based on a belief that science may not be sufficient to grasp a deeper meaning or an entire picture of nature, because the approach of science inherently depends on the segmentation of nature or on the elucidation of detailed mechanisms of local events. Although there is a potential thirst for global perspectives on the part of science, satisfactory methodologies toward the understanding of the whole are, unfortunately, not yet available. This gap is an inevitable situation of science at the present time, but science may never be able to find a satisfactory solution. Hence, philosophical and metaphysical perspectives should be incorporated to get to the heart of natural phenomena.

The metaphysicalization of science occurs through the following steps. The first step can be called "scientific abstraction": collecting, as widely as possible, scientific data on a targeted phenomenon, and then extracting minimal elements and basic characteristics that underlie the phenomenon. This step is thus based on scientific endeavor. For our study on immunity, this step has been completed in previous reports [3,80,81]. The second metaphysicalization step consists of contemplating the minimal elements and basic characteristics revealed through scientific abstraction in light of philosophical and metaphysical concepts and reasoning. More concretely, metaphysical concepts are incorporated into the description and understanding of natural phenomena, as revealed by scientific abstraction, and are used to grasp the essential feature of the phenomenon by carefully eliminating logical incoherence. This effort should contribute to the linking or fusing of nature and culture or present and past, which may eventually lead to a richer comprehension of nature or any problems in its totality. Thus, in the third step, the results and implications of the above analysis are needed to be actively transmitted to and communicated with people beyond science and philosophy. This "popularization" step could take various forms, for example, gatherings with scientists and non-scientists or publications aimed at the general public. Whatever form it takes, it is vital to encourage scientists and non-scientists to transform their views of nature or any phenomena.

Let us consider this proposal in the general framework of science and metaphysics. The task of over-viewing this field is not easy, given the vast amount of research completed thus far. Here, I will focus on three recent review studies. Soto analyzed the relationship between science and metaphysics from historical perspectives [82]. According to his study, the old wave essentially maintains that metaphysics works as a guide to scientific activities or makes science possible. There is a claim in the maximalist wave that because science aims to explain observable phenomena by accounting for unobservable realities, metaphysical elements are embedded in science, or science is metaphysical. In contrast, the new wave adopts a naturalistic approach, emphasizing that science is the best way to achieve knowledge of reality. Thus, in this wave, science is considered a guide to metaphysics or a restrictor of metaphysical activities. The recent minimalist version rejects metaphysics not based on science and pursues metaphysical approaches based on the epistemic, methodological, and ontological criteria established by science. Given this classification, the metaphysicalization of science seems to likely belong to the minimalist wave, although our approach emphasizes the use of metaphysical concepts to interpret scientifically revealed findings. Another study suggests that

at least two types of metaphysical approaches are present in science: scientific metaphysics and the metaphysics of science [83]. According to this classification, scientific metaphysics provides a metaphysical reflection on the nature revealed by science, whereas the metaphysics of science analyzes the assumptions, concepts, principles, models, and theories used in science, and the methods applied are often analytical and scientific. In other words, the object of the former is nature, while that of the latter is science. If this classification is applied to clarify the location of the metaphysicalization of science, it would seem to be closer to scientific metaphysics, although our proposal also includes actions toward the public. More recently, Guay and Pradeu analyzed how the interaction between science and metaphysics operates [84]. They observed two types of metaphysics of science. The first is “metaphysics applied to science”, wherein scientific findings can enrich metaphysical concepts, and the other is “scientific metaphysics”, in which science comes first and metaphysics arrives later. They then attempted to characterize the metaphysics of science by three-dimensional analysis, utilizing three axes, namely, descriptive versus revisionary metaphysics, a priori versus a posteriori metaphysics, and common-sense metaphysics, traditional metaphysics, and metaphysics of science. Although metaphysics of science can be descriptive and a priori, scientific metaphysics is typically revisionary and a posteriori. According to the authors’ metaphysical box model, our metaphysicalization of science overlaps with scientific metaphysics, but is open to approaches by descriptive and a priori metaphysics.

Although our metaphysical activities may not be a decisive factor for solving concrete scientific problems in daily activities, it is expected to influence the thought or imagination of scientists in a profound, albeit not immediately visible, way. The metaphysicalization of science accepts and highly respects science as it is currently operated, *prima facie*, independently of metaphysics, but expands the currently defined limits of science to an area that includes activities involving metaphysical and historical reflections on what current science produces. According to this proposal, an activity without philosophical and metaphysical contemplations of scientific facts will not be considered a complete science but only a partial or incomplete one. If the term “complete” sounds awkward, it can be replaced by the “ethics of knowledge” in the sense that a desirable form of knowledge *ought to* be derived from a combination of scientific reasoning and metaphysical reflection. Thus, not only scientists but also non-scientists should always keep this intellectual framework in mind. This proposal also implies that the third, “positive” stage of Auguste Comte’s law should be followed by a fourth, metaphysicalization of science stage. The whole scheme can be named the “Law of Four Stages”. Reaching the fourth stage of metaphysicalization of science may make it possible to describe or verbalize the essential feature of any phenomena that cannot be achieved by scientific endeavors alone. Whitehead discussed the relationship between science and philosophy in his Turner Lectures delivered in 1919:

The aim of science is to seek the simplest explanations of complex facts. We are apt to fall into the error of thinking that the facts are simple because simplicity is the goal of our quest. The guiding motto in the life of every natural philosopher should be, Seek simplicity and distrust it. [85]

Whitehead’s point is that while science seeks mathematical and concrete explanations of nature, philosophy should not stop there, instead going beyond what science has done. In other words, to reach the essence of any things or phenomena, one must proceed to metaphysical contemplation on scientific facts with logical reasoning. Their mental attitudes resonate with what metaphysicalization of science proposes.

Modern immunology, which started at the turn of the 20th century, has accumulated an enormous amount of information as to the structure of the immune system and the way the system works in physiological and pathological conditions. Most of these studies have focused on organisms that appeared at the later phases of evolution, mainly mice and man. If the objective of immunological studies is to find strategies to diagnose, prevent, and treat pathological conditions in man, studies on these organisms are undoubtedly necessary and sufficient. However, studying complex, complicated, and site-specific immunological mechanisms in a few highly evolved organisms can hinder the view of

the essential part of immunity because these systemic or synchronic analyses will reveal countless structural and functional elements involved in the process. In contrast, phylogenetic or diachronic analyses of the immune system, with an emphasis on the organisms at earlier evolutionary stages, may give important hints about the minimal requirements and essential elements of immunity that may have been blurred and missed in the analyses of mice and man, for example. Based on these assumptions, I have searched for the minimal elements in immunity. I concluded that the essential functional elements of the immune system could be summarized as sensing–interpreting–reacting–memorizing, and these elements have been conserved throughout evolution. Interestingly, these functional features are completely superimposed with those of the central nervous system of highly evolved organisms.

All living organisms must have an immune system because it is impossible to live and survive in this hostile world without one. Given that the immune system is integrated into the organismal whole, it is naïve to think that it is just a defense mechanism. It may extend to functional attributes at the level of an entire organism. Following logical contemplations on the quasi-totality of findings on immunity, I conclude that immunity is involved in regulating the balance between physiology and pathology and is essential for life and the existence of living organisms. While searching for metaphysical concepts describing these characteristics, I learned of Spinoza’s fundamental concept, *conatus*, an activity for the preservation of beings. Because this concept was superimposed on the fundamental features of immunity, it may help reveal the hidden aspects embedded in the essential core of immunity. In the following section, I discuss immunity from the perspective of the *conatus* of Spinoza.

4. Immunity in View of the *conatus* of Spinoza

Since the discovery that the immune system is present in bacteria and archaea as the CRISPR-Cas system [5–12], a consensus has been reached that immunity emerged when life forms first appeared on earth. Without an immune system, no living organisms can live or survive. Immunity is a prerequisite for life and may even constitute the essential condition for life because organisms without an immune system are, in fact, not living.

The immune system’s activity is not restricted to prototypic activities of defense against microorganisms but extends to non-immunological functions even in the most primitive organisms: bacteria and archaea [86–88]. In highly evolved organisms, the immune mechanism is interwoven with the workings of other systems, such as the nervous and endocrine systems, to form what is often called the psychoneuroimmune or psychoneuroendocrinoimmune networks [58,89]. As research has progressed, intersystemic boundaries have indeed become increasingly ill-defined, such that the boundary of the immune system has reached almost the entirety of an organism [53–58]. In other words, immunity functions as an organismal whole, not as an isolated system in an organism. Given these current understandings, it is time to thoroughly reexamine the existence and definition of the immune system and reflect once again on the ontological characterization of immunity with metaphysical concepts.

The importance of immunity’s ability to control positive and negative effects in organismal existence and survival brings to mind the notion of *conatus* introduced by Spinoza in his text *Ethics* [90]. This term is derived from Latin and can be translated as “effort”, “endeavor”, or “striving”. Spinoza recognized an essential inner force in each being aimed at preserving its existence and used the term *conatus*, one of the principal concepts of his philosophy, to express this quality. At the time of Spinoza, immunology was inexistent. Since the turn of the 19th century, evolutionary thoughts, instead of fixism, have been proposed notably by Lamarck [91] and Darwin [92]. The influence of these ideas extends to almost all areas of biology, as Dobzhansky famously noted, “Nothing in biology makes sense except in the light of evolution” [93]. Immunology is no exception. It has significantly transformed since the turn of the 20th century, and the paradigmatic clonal selection theory of Burnet, concerning specific antigen recognition and activation, immunological tolerance (avoidance of autoimmunity), and memory formation, was a replica of the Neo-Darwinian theory of mutation and selection [35]. At the other end of the evolutionary tree, the bacteria’s immune system incorporates an environmental

element into the host genome and transmits it to daughter generations, suggesting that the CRISPR-Cas system is a case of Lamarckian inheritance [94]. Bacteria are also under evolutionary pressure via an arms race with bacteriophages [95], and bacteriophages, in turn, even use the bacterial defense system CRISPR-Cas to counteract with bacteria [96]. These examples are nearly ubiquitous in immunology. It is thus possible to discuss immunity from evolutionary perspectives. However, in this study, I aim to search for essential features of immunity in metaphysical terms rather than to describe immunological features in mechanical terms. For this purpose, metaphysical ideas need not necessarily be modern. Thus, I chose the *conatus* of Spinoza to reach the core of immunity, as to my knowledge, immunity has never been examined in this context.

I will firstly examine Spinoza's thought on *conatus*, and then assess how immunity can be viewed from the perspectives of this concept. In Part III of *Ethics*, "On the Origin and Nature of the Emotions," Spinoza defined the *conatus*. In Proposition VI, he writes, "everything, in so far as it is in itself, endeavours to persist in its own being." This endeavor to persevere in its own existence is the *conatus*, and it applies to each and every being. Furthermore, Proposition VII states that, "the endeavour, wherewith everything endeavours to persist in its own being, is nothing else but the actual essence of the thing in question." In other words, all beings are naturally endowed with a drive to persevere in their own being, and the *conatus* does not just happen to be but constitutes the essence of any being. Moreover, Proposition VIII affirms that the *conatus* does not involve finite time but indefinite time. The natural striving continues to exist as long as the being exists or until it is disturbed.

However, there is a problem with Spinoza's notion of *conatus* when we try to apply it to immunity, because the attempt to persevere in its own being concerns every being, including inanimate things. From the dualistic perspectives, a problem arises regarding how to explain the difference in *conatus* between inanimate things and living organisms. Spinoza's position is panpsychist in that he saw mind in matter or thought mind and matter are two aspects of each existence, or what he called substance. Thus, there is little problem in explaining how to emerge the mental from the inanimate. In this respect, Spinoza relates this notion to the faculty of the mind, specifically in humans, in Part III, Proposition IX:

The mind, both in so far as it has clear and distinct ideas, and also in so far as it has confused ideas, endeavours to persist in its being for an indefinite period, and of this endeavour it is conscious.

Thus, the *conatus* includes the mind's faculty of both endeavoring to persevere in the organism and to become conscious of this endeavor. In Part III, Proposition IX, Scholium, Spinoza further describes distinct forms of the mental tendencies of *conatus*.

This endeavour, when referred solely to the mind, is called will, when referred to the mind and body in conjunction it is called appetite; it is, in fact, nothing else but man's essence, from the nature of which necessarily follow all those results which tend to its preservation; and which man has thus been determined to perform.

Further, between appetite and desire there is no difference, except that the term desire is generally applied to men, in so far as they are conscious of their appetite, and may accordingly be thus defined: Desire is appetite with consciousness thereof.

According Spinoza, the *conatus* of a living being applied only to the mind is called "will", and that applied to both the mind and body is called "appetite". It may have been inescapable to limit "appetite" to human beings during Spinoza's time, but given recent developments in cognitive science, the faculty of "appetite" can be expanded to other species and interpreted as fundamental activities broadly distributed across living organisms. Interestingly, there is also a faculty called "desire", which represents a condition in which living organisms become conscious of "appetite". It is thus plausible that "desire" comprises activities that are more sophisticated and higher-ordered than those of "appetite". The definitions of "appetite" and "desire" are not further detailed in Spinoza's philosophy.

As far as the physical aspect of *conatus* is concerned, any living being attempts to avoid injury, and when injured, they try to restore themselves and endeavor to persevere in their own being and to resist invasion or domination by other beings. The *conatus*, in this regard, overlaps with the activity of immunity. The mental aspects of *conatus*, namely “appetite” and “desire”, align with the present-day definition of two levels of consciousness. One consists of the qualitative or experiential awareness of your environment and your body, and the other is recognition of that awareness. Ned Block pointed out this distinction by naming the former phenomenal consciousness and the latter access consciousness [97]. Later, Gerald Edelman similarly divided consciousness into “primary or sensory” consciousness and “secondary or higher-order” consciousness [98]. Edelman makes it clear that secondary consciousness involves the world in the past and the future, self-reflectiveness and metacognition. In contrast, primary consciousness only concerns the present and immediate past, or, as he put it, the “remembered present” [99], but not the future of the world around us. Although secondary consciousness may be limited to man, primary consciousness extends to some animals. Some researchers use the term “self-awareness” or “cognition” to refer to the higher-order consciousness and simply apply the term “consciousness” to the primary experiential consciousness. No matter what term is used, at least two levels of mental activities are commonly understood: primary or sensory consciousness and secondary or higher-order consciousness. Interestingly, these two levels of consciousness correspond very well to Spinoza’s “appetite” and “desire”, respectively.

As discussed above, the notion of “appetite” concerns both the physical and the mental. The present state of our understanding of immunity indicates that the immune system is involved not only in the host defense but also in the regulation of neurological and psychological conditions through neural, hormonal, and immunological networks [60–64]. Furthermore, the function of immunity may be closely associated with the cognitive process of the central nervous system, which is omnipresent in living organisms [3,19,20,80,100]. The success of any discussions depends on the definitions of the terms used. To maintain consistency with previous publications [3,4,80], in this discussion, I use the term “cognition” to indicate a function that consists of the reception and integration of external information, action according to the integrated information, and memory of that experience. Biological definitions such as this should eliminate confusion linked to interpretations of subjective elements and may unveil unexpected aspects of nature that are often hidden by anthropocentric and automatic thoughts. Given its cognitive aspect, immunity present in all living organisms can be viewed as a functional activity endowed with both mental and physical attributes. If, as Spinoza claims, the essence of any being lies in the *conatus*, and the conative effort in the form of “appetite” is identified with immunity, then immunity becomes an essence, if not *the* essence, of living beings. The close association between immunity and life also fits well with the conclusion reached thus far.

For Spinoza, human beings in nature are subjected to causal necessity just like any other beings. In contrast to Descartes’ substance dualism, Spinoza argues that there is one thing in nature, and the mental and the physical are inseparable (*Ethics*, Part II, Proposition XI). Deleuze defines Spinoza’s principle as parallelism and distinguishes three different types [101]. The term “parallelism” is not Spinoza’s but seems to have been coined by Leibniz [102]. According to Steven Smith’s analysis of Deleuze [102], first, parallelism implies a formal correspondence or symmetry between the two modes. Spinoza defines mode as “the modifications of substance, or that which exists in, and is conceived through, something other than itself” (*Ethics*, Part I, Definition V). Two things are considered to correspond with one another if they share a similar or related function. This similarity is called “correspondence by functional equivalence”. Second, in equality between the two things, neither is superior to the other. Third, parallelism implies not only a formal symmetry but also a literal identity of the mental and the physical. These two substances are not independent but the same substance with two faces, so to speak. These criteria are beneficial in discerning similarity or identity between two entities: for example, the immune system and the nervous system, or the immune system of one species and the system to be identified in another species. Thus, it is easy to understand the correspondence

between the human immune system and the bacterial immune system by the first criterion, which refers to functional equivalence.

By the same token, the immune and nervous systems share basic functional elements. It may not be so surprising then to speculate that the two systems functionally correspond to one another. If the premise that cognitive ability is essential for the survival of living beings is acceptable, the immune system may substitute for the nervous system in bacteria and archaea without a nervous system identified thus far. These considerations and the understanding that immunity is omnipresent in the realm of living beings are compatible with the idea that the basic function of immunity corresponds to Spinozist “appetite”, which is, by definition, expressed in broader living organisms and includes physical and mental activities. Furthermore, this conclusion also fits very well with recent developments that immunity is an expression of whole organismal functions extending to mental activities [53–58].

Antonio Damasio also considered the notion of the *conatus* in his studies of homeostatic regulation of humans and unicellular organisms. His version of the *conatus* is concrete and includes a variety of chemical molecules conveyed to the brain and electrochemical signal transmissions that generate feelings and the impetus for self-preservation. Damasio thinks that *conatus* is rooted in the brain and in the neurobiological regulatory activities; however, he sees emotional reactions or the essence of the process of emotion in unicellular organisms without a brain, such as *paramecium*. This reasoning is self-contradictory and does not accord with the *conatus* of Spinoza, which refers to all existence, including inanimate things. According to his tree-like schemes of emotions, immune responses, along with basic reflexes and metabolic regulation, are placed at the basal level of the trunk, with emotions and feelings at the top branches [103]. This hierarchical structure reflects anthropocentrism. If we extend our view to a broader world of living organisms, the scheme of Damasio must be modified. As examined in previous reports [3,80,81], the position of immune responses in bacteria is not low, but rather central to the existence of the organism, and thus should be placed at a higher level.

Another important aspect of *conatus* must be considered for a deeper understanding of immunity or any other phenomena. Spinoza notes a close relationship between the conative power and moral considerations, as mentioned in Part III, Proposition IX, Scholium:

It is thus plain from what has been said, that in no case do we strive for, wish for, long for, or desire anything, because we deem it to be good, but on the other hand we deem a thing to be good, because we strive for it, wish for it, long for it, or desire it.

According to this note, nothing is inherently good or bad, but the criterion of the two is relative, depending on whether or not a certain thing is good and useful to us. Furthermore, in the Preface of Part IV, “Of Human Bondage, or the Strength of the Emotions”, Spinoza affirms this claim by the following:

As for the terms good and bad, they indicate no positive quality in things regarded in themselves, but are merely modes of thinking, or notions which we form from the comparison of things one with another. Thus one and the same thing can be at the same time good, bad, and indifferent. For instance, music is good for him that is melancholy, bad for him that mourns; for him that is deaf, it is neither good nor bad.

In Proposition XXXIX of Part IV, Spinoza writes on the human body from this perspective.

Whatsoever brings about the preservation of the proportion of motion and rest, which the parts of the human body mutually possess, is good; contrariwise, whatsoever causes a change in such proportion is bad.

Spinoza understands that the human body consists of parts, and for the preservation of the body, they must communicate with each other by motion. He thinks that the balance between motion and rest guarantees the existence of a human body. Furthermore, whatever brings about the preservation of the proportion between the two conditions is good, and whatever brings about a change in the proportion

is bad. This idea is consistent with the current understanding of the pathological conditions of all living organisms from the perspective of the equilibrium of contrasting forces or factors. What is more important is the indication that the effort of maintaining balance is good, and the things that disturb the balance are bad. These thoughts of Spinoza introduce a moral aspect to the concept of *conatus*. If the idea that the essence of immunity corresponds to Spinoza's "appetite" is valid, then immunity must be scrutinized in light of moral or normative considerations. In the next section, I will further investigate immunity from the normative perspective of Canguilhem's philosophy.

5. Immunity in Light of Canguilhemian Philosophy

Immunity is adaptative, and so is the immune system. In general, the term "adaptability" used in biology is understood as the ability to change to fit or cope with unexpected disturbances in the environment. Thus, adaptative capacity is one of the essential characteristics of life and critical to the evolutionary process and organismal survival. Adaptability can be discussed in terms of what should be desirable for the organism, although this argument may possibly be not acceptable from a strictly scientific perspective. If immunity, inseparable from life, is viewed as implementing mechanisms for *conatus* in the form of "appetite", it is reasonable to hypothesize that an element of norm or value may be embedded in immunological functions.

The term "normativity" is used in various domains, including philosophy, social and natural sciences, law, and economics, and has different meanings in each respective field. Thus, it is challenging to discuss normativity on a single or fixed basis. However, it is generally used to describe human behaviors to provide a standard for judging whether certain actions are good or permissible. The issue is what ought to exist or be done in a specific situation, but the term is also used in a nonevaluative or descriptive fashion. Because the focus of this study is a biological phenomenon, I searched for a philosopher to serve as a reference in this context. George Canguilhem studied the problem of normativity in physiology and pathology in human biological conditions and proposed unique interpretations thereof, which are pertinent to this discussion and may introduce a new perspective to immunity. For this reason, I thought that he would be an excellent but not necessarily solitary source to reflect on the implications of normativity in biological reactions leading to a balanced or disturbed state. As it turned out, reflection in light of Canguilhemian normativity was fruitful and added another dimension to our understanding of immunity's essential features.

Canguilhem expressed his thoughts on the problem of normativity in his magnum opus, *The Normal and the Pathological* [104] (abbreviated as *NP* in the following discussion). He focuses on the normativity with a sense of creativity. In his first work, *Essay on Some Problems Concerning the Normal and the Pathological*, written as a doctoral thesis in 1943, Canguilhem presents an explanation of the concept of the normal and the pathological and reflects on concrete human problems by addressing the questions related to medicine (*NP*, 27–229). Canguilhem maintained that the normal is a value of life determined by each individual, not by statistical figures. He understood that life is a normative activity, and the actor should establish the norms rather than the witness subordinate to the one who installs the norms. However, a normative activity is often used in the latter sense. The normal is highly individualistic and concerns individuals' capacity to be active and to change the relationship with environments or even to invent their own norms. This biological activity is normativity and can be life itself. Canguilhem also proposes the dynamic polarity of life as a new concept and normativity as a controller of this polarity. He agrees with Kurt Goldstein and Henry Sigerist, saying that the biological norm is always individualistic, and the condition of each patient must be carefully followed without relying on an average obtained from the data of unrelated individuals collected at a given time (*NP*, 181–182). As Goldstein noted, Canguilhem shows that being sick is not the lack of a norm but represents the chance to create a new norm of living, although it may be inferior to the previous one (*NP*, 183). With a positive act of self-invention of the norm, I think that one could be freed from psychological stress resulting from passive reliance on figures calculated from a population, giving us a sense of control over the body and of self-fulfillment.

Life is in perpetual dynamism, and the border between the normal and the pathological becomes obscure at the population level because the boundary between the two conditions, based on numbers derived from a group of unrelated individuals, does not reflect individual and temporal variations. However, the border becomes clearer and more evident when one consecutively follows the data of an individual. Thus, historical analysis becomes inevitable. The pathological condition gives an organism the ability to adapt to changes in the environment and establish a new norm. The pathological is not confined to a single part or a single function of the body but reshuffles the whole body and individual. Considering disease as an “effort” by man to obtain a new equilibrium, Canguilhem argues that there is a continuity between the pathological and the normal and an interdependence of all elements and all functions in the body. In other words, a disease state should be viewed as an organismal reaction, not as a local event. As discussed above, the experimental data accumulated since the time of Canguilhem consolidate his supposition. He also states that disease is not just a fact of decrease or increase but a positive, innovative experience in a living being, and that disease is not a variation on the dimension of health but is a new dimension of life (NP, 186).

In a discussion about biological polarity, natural selection, and natural medicinal activity (*vis medicatrix naturae*), Canguilhem cites Émile Guyénot:

It is a fact that the organism has an aggregate of properties which belong to it alone, thanks to which it withstands multiple destructive forces. Without these defensive reactions, life would be rapidly extinguished. [. . .] The living being can instantaneously find the reaction which is useful vis-a-vis substances with which neither it nor its kind has ever had contact. The organism is an incomparable chemist. It is the first among physicians. The fluctuations of the environment are almost always a menace to its existence. The living being could not survive if it did not possess certain essential properties. Every injury would be fatal if tissues were incapable of forming scars and blood incapable of clotting. (NP, 130)

In this context, the term “defensive reactions” is used rather than “immune responses” or “immunity”. Canguilhem also adds:

But disease is not simply disequilibrium or discordance; it is, and perhaps most important, an effort [HY’s italics] on the part of nature to effect a new equilibrium in man. Disease is a generalized reaction to bring about a cure; the organism develops disease in order to get well. (NP, 40–41).

His version of a major “effort” of nature is most likely another name for immunity and the *conatus* (effort) of Spinoza. This interpretation reflects the view of Élie Metchnikoff that disease, as a form of inflammation, is a manifestation of the body’s positive responses to microorganisms, rather than the passive, defeated conditions in a world of disharmony. The essential role of immunity is conceptualized as an activity that defines and maintains organismal identity and integrity [105]. As in Hippocratic medicine, Canguilhem believed that the concept of disease is no longer ontological but dynamic, no longer localizationist but totalizing. Nature, including man, is in harmony and equilibrium, and disease is interpreted as the disturbance of this harmony and equilibrium. More importantly, disease is an effort on the part of nature to bring about a new equilibrium in man and is a generalized reaction to accomplish a cure (NP, 40–41).

Canguilhem rarely spells out “immunity” or “immune responses” except for the comparison of antibody-mediated immunity between normal immune responses and allergy or anaphylaxis, as an example of the polarity of life (NP, 206–207; 211–212). The presence of antibodies characterizes both conditions, yet the outcomes of the responses are in opposition: one is protection and stabilization, while the other is catastrophe and sometimes death. Canguilhem wrote the first version of *Essay on Some Problems Concerning the Normal and the Pathological* (1943) before the publication of the clonal selection theory, the paradigm in immunology developed by Frank Macfarlane Burnet [35], but long after the work on antibodies by Emil von Behring [31] and Paul Ehrlich [30], and on phagocytes by

Élie Metchnikoff [29]. Although his discussions on immunity are limited, Canguilhem's observation suggests that the normative activity involved in regulating the biological polarity may reside in immunity. Given that life and immunity are inseparable, it may be possible to say with Guyénot, as cited above (*NP*, 130), that all living organisms are incomparable immunologists.

More recently, based on Canguilhem's definition of biological normativity, there has been an examination of whether normativity is a genuine capacity of the organism and whether a normative capacity is observed at different levels of organization—for example, systems, organs, molecules, and genes [106]. The author concluded that the normative capacity is observed in the organism and the immune system but is not necessarily shared by other levels of organization—for example, molecules and genes. However, this issue should be handled carefully. One of the reasons is that vertebrate immune systems are well examined but are special in view of the immune systems observed in the entire living world. If one discusses these problems by examining only vertebrate systems, it is quite easy to lose sight of the essential part of the matter. This problem was a lesson learned from a phylogenetic analysis of the immune system [3,4,74]. Examination of other species, including primitive unicellular organisms, may provide a clue to this problem. For example, a phenomenon called autoimmunity must be avoided because it can destroy the organism. When a self-destructive situation arises in bacteria, the genes that make up the immune system, CRISPR-Cas, avoid self-reactivity by adaptive mechanisms at the genetic level [88,107]. The genetic system can adapt to changes in the internal milieu, and it looks like creating new norms to my eyes; genes are neither passively ordered nor unable to act according to these norms. Based on the discussions above on the normal and the pathological, it is reasonable to propose that immunity supports life's normativity and controls biological polarity. Together with the discussion in the previous section, the essential feature of immunity can be superimposed on Spinoza's "appetite" in terms of their normative capability and controlling ability of biological polarity.

6. Conclusions

As the work progresses to examine the lifestyles of typical living organisms from the perspective of immunity, the similitude in the principle of immunity among living organisms, from bacteria to humans, becomes striking, despite apparent differences in the molecular mechanisms and the structures that support those mechanisms. Given that an immune system is indeed present in all living organisms and that organisms cannot live without one, the presence of an immune system can be taken as a prerequisite to life and survival and as one of the criteria of life. Immunity constitutes the most ancient machinery that executes recognition and keeps memory, as evidenced by the CRISPR-Cas system in bacteria and archaea that appear to lack a nervous system [3]. These neural-like functions embedded in immunity, from bacteria to man, prompted me to examine the philosophical implications of immunity, with special reference to the Spinozist concept of *conatus*, because this concept implies the inner force towards the preservation of existence. Furthermore, the normative activity controlling biological polarity is implicated in *conatus* such that the effort of maintaining balance is good but disturbing balance is bad. Given philosophical reflections on the biological normativity from the perspective of Canguilhemian philosophy, immunity can balance polarizing forces towards health and disease. Immunity is equipped with the characteristics of the physical and mental attribute of *conatus* (the "appetite", to be precise), which is broadly distributed in living organisms. Thus, I propose that the essential element of immunity includes something related to the mental or conscious activity that performs recognition and generates memory, in addition to the physical activity that balances biological polarity.

The mental or subjective world is limited to the one who senses it and may never be knowable to others. Thus, there is an inherent difficulty in discerning whether other organisms are conscious. Because consciousness has been thought to be restricted to highly evolved animals with complex brains, specifically, to human beings, the term "consciousness" was originally introduced to describe the state of awareness of external and internal worlds in humans. Thus, we are accustomed to thinking about the consciousness of other living beings by simple anthropocentric speculations, automatically

concluding that they do not have it. In a paper entitled “What is it like to be a bat?” [108], Thomas Nagel demonstrated that objective knowledge about the structural and functional characteristics of the bat brain would be insufficient to get the “feel” of how a bat experiences the outside world. In other words, the physical understanding of a phenomenon or an experience of a living organism does not explain how it is experienced or felt by the organism. This problem is named the “explanatory gap” [109]. Many attempts have been made to close or narrow this gap in the philosophy of mind, but it still remains unbridged [110–113].

However, even with the difficulties involved in explaining the relationship between the physical properties of the neural machinery and the subjective experiences of consciousness, neurobiological, behavioral, and philosophical studies of living organisms suggest that the “phenomenal” or “primary” consciousness may be a shared property of almost all living beings. Based on the lesson from phylogenetic studies of the immune system, we learned that the structural components of a particular function can be extremely different from species to species. The problem of consciousness is no exception. Although I agree that we humans are most likely the living beings with the highest levels of consciousness and cognitive ability, the scenery of nature will drastically change if we drop the anthropocentric worldview that is so prevalent today and makes it almost impossible to be conscious of that influence on our thoughts. We do not know whether and when science can ever handle the inner world of subjectivity. Therefore, it may be reasonable and safe to consider, with reservation, the problem of consciousness in other living organisms. Furthermore, it becomes much easier to discuss the problems of consciousness on the common ground if one adopts a biologized, more inclusive definition to describe subjective activities. Take, for example, the proposition by Alain Prochiantz, which suggests that a mental activity such as “thinking” can be defined in purely biological terms as an adaptative relationship of an individual or species to the milieu [114].

Thrown into a harsh milieu, we living organisms are compelled to adapt under evolutionary pressure. To put it boldly, all living organisms must “think” in whatever way they can to live and survive. The immune system perceives information from the exterior world, integrates it to react adaptively to the original environmental cue, and stores that experience as a memory for future use. If we accept the logical contemplation and reasoning presented in this study, the immune system is cognitive, and living organisms indeed think through this system. In conclusion, the essential feature of immunity includes something closely related to the conative activity with normative connotations that regulates cognition and balances biological polarity, expanding previous proposals of the cognitive paradigm of immunity [40,41,115–117]. These findings also suggest that immunity can be understood more deeply from the cognitive perspective.

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