



The Immune Self: Practicing Meaning *in vivo*

Yair Neuman

*Department of Education, Ben-Gurion
University of the Negev, Israel*

Abstract

The immune self is our reified way to describe the processes through which the immune system maintains the differentiated identity of the organism and itself. This is an interpretative process, and to study it in a scientifically constructive way we should merge a long hermeneutical tradition asking questions about the nature of interpretation, together with modern understanding of the immune system, emerging sensing technologies and advanced computational tools for analyzing the sensors' data.

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1. A philological prelude

The online Etymological Dictionary [<http://www.etymonline.com/>] teaches us that the root of "self" is "separate, apart", which means that the Proto Germanic source of the sign "self" designating "one's own person, same" is grounded in the activity of producing a "difference that makes a difference" (Bateson, 2000).

The first definition of "self" in the Oxford English Dictionary teaches us another important lesson about the way in which the meanings of signs have evolved through the rather short period of our cultural evolution. The OED defines self as: "A person's *essential* being that distinguishes them from others, especially considered as the object of *introspective* and *reflective action*" (emphasis mine). While the Proto Germanic source says nothing about "essence", the OED's definition is a product of reification in which the most basic activity of constituting a difference that makes a difference turns into a mysterious essence, which is also the object of introspection and reflection by another no less mysterious "essence". This essentialist definition of the self could have not been produced other than in Europe, where the monitoring and regulating function of the Catholic Church has been

replaced by an internal compass, a super-ego that introspects and reflects on man's soul, which is in its turn "self-conscious" in a very unique European and Protestant sense.

One may question of course this "cultural relativism" in which the meaning of "self" is determined by a symbolic network of a given historical period. Why do we need this cultural relativism one may ask? Can we imagine a person without a self? Can we imagine a person without motivation? or consciousness? Can we argue that people got their self only when this term has been baptized in the Protestant Churches of Europe? The naive realist may further use the doomsday weapon: The analogy to Newton's law of universal gravitation. Do you believe, he may poignantly ask, that Newton's law existed only after Newton had formulated it? Did apples fall differently before the brilliant Sir Isaac formulated the law in mathematical terms? You would probably not offer such a foolish argument, so why argue that the European culture has invented something that probably exists in each and every human being? My dear naive realist, we may reply, haven't you realized the difference between an apple and a human being? While an apple exists "in and for itself" a human being thinks, is motivated, and behaves according to the intricate symbolic Web in which s(he) is woven. As argued by Bakhtin, we are all unique but never alone, and as we are always interacting with others who bring us to the world and frame our perspectives, we are obliged to reflectively acknowledge the schemes that frame our mind. For the ancient Greek the most powerful motivating force was the code of honor. Was he "motivated" the same as the rational capitalist who considers his motivation in terms of maximizing profits? The answer is probably "No" and the reason is that the ancient Greek did not behave indifferently to the cultural frames that guided his behavior and the understanding of his behavior.

This short philological prelude in a paper that deals deal with the immune self does not aim to propagate a form of cultural relativism that I totally reject, but to reflectively and critically point to the cultural and contextual nature of the concepts that guide and mediate our intellectual activity. There couldn't be a serious discussion of the "immune self" without taking into account the cultural evolutionary baggage through which the concept of "self" has acquired its different senses.

2. The immune self: What and How

As the concept of the "immune self" has been the subject of intensive theoretical analysis, I have no intentions whatsoever to review this literature but only to present a modest perspective on the immune self. Following my previous work on the subject (Neuman, 2008), I will in large try to avoid the "what" question (What is the immune self?) as this question almost inevitably leads to the essentialist pitfall. Instead, I will try to propose to conceptualize the immune self in a way that may be theoretically intelligible and at the same time relevant for producing new research questions. As suggested by Efroni and Cohen (2003), a scientific theory should not

be judged only by one limited criterion, which is its ability to answer scientific questions, but also by its ability to produce new research questions. Adopting a non-conventional organismic metaphor I may say that similarly to an organism, an idea should not be studied only by the solutions it represents in face of evolutionary forces, but also through the potential promise it presents as a source of renovation and resilience for the generations to come.

Let me start by returning to the old original sense of "self" as an activity of producing a difference that makes a difference. If we adopt this sense then we do not make "a categorical error in assigning human description to lymphocytes and antibodies" (Tauber, 1996, p. 8). Tauber's criticism against the anthropomorphism of the "immune self" may be relevant if we apply the modern protestant sense of the self to the immune system. However, if we adopt the old idea of the self as a boundary constituting activity, then there is no categorical error in using the concept of "self" for describing the activity of lymphocytes and antibodies, as these are components that clearly play a role in constituting and maintaining certain boundaries essential for the survival of the organism as a differentiated unit of activity. One should notice that this idea does not involve a circular argument as it involves a conceptual shift between several realms or logical types. The self is the "organism's systemic closure that defines it for all practical reasons as a differentiated unit of activity/analysis" (Neuman, 2008, p. 96). Without our pre-theoretical observation that certain objects exist, and therefore are differentiated from the rest of the world, we can have no theoretical discussion whatsoever. Given the existence of certain objects we can ask how they come to be differentiated in our mind, which is an epistemological/psychological question, and how do they come to be differentiated in the world regardless of our contemplation. In other words, the second question is a kind of ontological question. While nonliving entities exist "in and for themselves" as described by Husserl, organisms continuously struggle to actively maintain their differentiated existence. Each and every organism struggles on a daily basis and from one moment to another to constitute and maintain its differentiated existence.

As we can see from the above discussion, a minor shift in semantics has clear pragmatic consequences. If the self signifies the activity of boundary constitution, then the question is not "What is the immune self?" but "How does it work?" Here again we meet a version of the essentialist concept suggesting that there is an built-in genetic barcode that allows the immune system to maintain the boundaries of the organism and to constitute its systemic closure. Like a can of beans in the supermarket, each and every organism, according to this genetic reductionist explanation, has a well-defined barcode, a fingerprint that signifies its unique identity and is used for differentiating the organism from other organisms. Such a genetic barcode (the MHC for instance) may play a certain role in constituting systemic closure the same as a person's name signifies a certain aspect of his identity. However, the genetic barcode cannot fully explain the systemic closure of the organism and its identity the same as a person's name may designate him but cannot be mi-

sinterpreted as his identity. The sign is never the signified. In fact, the genetic reductionist perspective of the immune self echoes some naive, even primitive one may argue, mythical concepts identifying the sign with the signified. The horror of mentioning the devil's name, in some cultures, results precisely from this concept and the idea that pronouncing the devil's name might bring the ripper to the scene.

The genetic reductionist concept is wrong even for the simple fact that our body, for instance, hosts a wealth of microbial life that cannot pass the barcode criterion. Moreover, even some parts of our self cannot simply pass the barcode test. A trivial example that I use in my book concerns the tolerance of the male body to sperm cells. Sperm cells are produced in the male's body long after his immunological identity, whatever it is, has been established in childhood. These "newcomers" are not simply tolerated by the immune system because they have the genetic barcode of the self. A testicular trauma such as kicking someone in his balls may lead the immune system to identify the sperm cells as associated with infection and to attack them regardless of any identity card they may hold. In the dynamic and symbiotic context of the living organism, the barcode model is too rigid for explaining systemic closure, the same as the identity of a city cannot be explained by the fact that only those holding a certificate identifying them as citizens of the city are allowed to enter and live there. Such a policy would have prevented us from hosting *E. coli* in our colon despite the valuable symbiotic relations that we maintain with this bacteria. In other words, and as Darwin teaches us, the organism is a dynamic thing. A rigid essentialist form of identity would have banned any change, symbiotic relations, or contextual flexibility, which is of prime importance. Well argued! declares the reductionist, so let's throw the immune self and just leave the ... non-self. This is precisely the suggestion underlying Burnet's Clonal Selection Theory (CST). Burnet suggests a very appealing idea according to which lymphocytes with reactivity against host components are destroyed and therefore the immune system identifies and attacks only the non-self. The idea is appealing in a very basic sense: An immune system that recognizes the "self" is in danger of attacking its self and therefore evolution has naturally produced an immune system blind to its self but sensitive only to the non-self. As we know, there is no army without an enemy but for Burnet the immune system is an army without a homeland to defend. The only minor problem with Burnet's appealing thesis is that it is wrong. As argued by Cohen (1994), the immune system knows to recognize itself. Cohen convincingly presents this thesis and as an alternative introduces a dialogical approach according to which self and non-self are complementarily represented in the immune system. There is no self without non-self and vice versa. The theoretical challenge to be addressed is how this delicate balance between the self and non-self is dynamically and contextually created and maintained. Here we get to the idea that the immune system is a meaning-making system (Neuman, 2004).

3. The immune system is a meaning-making system

The challenge facing the immune system is not a mechanical challenge of matching a key to a lock, a receptor to an antigen. This powerful lock-and-key metaphor cannot explain the complex behavior of the immune system (Cohen, 2000; Neuman, 2008). The challenge as I see it is a challenge of interpretation, of meaning making. To explain this point I will use natural language. However, by describing the immune system as a meaning making system I do not simply adhere to a linguistic metaphor. I don't use the conceptual metaphor: The immune system is like natural language. In contrast, I argue that meaning making in its different forms underlies both the activity of the immune system and of natural language. To explain this idea let me start with the polysemy of the sign. Signs in natural language can be polysemous, meaning that they can have different senses in different contexts. For instance, Bass can be used to describe a kind of Fish but also Guitar Bass. There is no meaning encapsulated in the sign itself. It is not a barcode, it does not correspond to a cherished sense living far away in the realm of Platonic ideas, and the form of the sign is arbitrary as insightfully realized by Saussure. Polysemy is a defining characteristic of natural sign systems from human language to the immune system, and it inevitably calls for interpretative activity. If the same sign can mean different things in different contexts how do we know to assign the proper meaning to the sign? The heart of interpretative activity lies in our need to resolve this problem of sense disambiguation. However, let us take a step backward in order to try and explain why polysemy exists. To explain this phenomenon let us recall the seminal work of Zipf (1949). Zipf identified the inherent conflict in every act of communication. If I use signs to communicate some meaning then my economic and energetic interest is to minimize my effort. This interest does not result from ideological laziness. For generations of organisms the world has been (and still is) a tough place, a place where resources are not given for free. In this context, a first principle evident in different forms of biological behavior is the optimal expenditure of energy. In this context, the "sender" would have preferred to communicate all possible intentions, ideas, emotions, or whatever communicable in a single word lexicon! Why should the brain be occupied by building, maintaining, and using a large mental lexicon when one can use a single magic word for everything? The same is true for sign processes in the biological realm. If an antigen, a virus, for instance, can be described in mechanical terms as a "key" and if it has the free choice to design itself, then it would have probably been like the thieves' famous key that can potentially open every lock. A key that can open every possible lock is the same as a single word lexicon that can gain the appropriate response with a minimal expenditure of energy. The problem is the conflicting interest of the "receiver" who would like to invest the minimal amount of energy in interpreting the sign. Trying to understand the meaning of a single word lexicon would have consumed enormous effort of mapping the sign into all possible entities and actions in the world. For the receiver, the interest is clear: a sign for every possible signified entity and action. This demand is unrealistic due to the effort required from the sender to hold an enormous, even astronomical, lexicon con-

taining, for instance, different signs for the "I"; the "I" that denotes the person I am now but also the person I was yesterday when my mood was different, and so on. The same is true for the immune system. If the receptor site could have been analogically described as a lock, then this lock should have been a rigid pattern that can easily identify any vicious intruder. In fact, the antibody does have a more rigid part, a fixed "lock", but this is only a part of the story as the flexible part of the antibody is necessary in order to follow the rapid pace in which the various potential antigens change their "lock" in order to survive. In this evolutionary game between the conflicting energetic demands of the "sender" and "receiver", the polysemy of the sign is a kind of resolution between the two extreme positions. I don't argue that this is an agreed, rational, and conscious result of a social contract between 'receivers' and 'senders' in the biological realm and emphasize the fact that the same biological agent may function both as sender and as receiver. However, we can definitely consider the polysemy of the sign, in both the realm of natural language and the realm of immunology, as an optimal solution emerging under the constraints of the interlocutors' conflicting interests. The price of this optimal and emerging solution is the need to interpret the sign-in-context. Think about this evolutionary game in the context of host and parasite relationships. The host and the parasite mutually recognize each other. The interest of each of the interacting parties is to recognize the other with minimal effort while making sure their social contract of mutual support is still valid. For instance, the parasite may present to the host a single biological signature identifying him as one of the good guys. However, such a position would have demanded from the host enormous effort in interpreting this sign under changing contextual circumstances. The idea is that a single, one-sense signal identifying the parasite as a legitimate guest might not be flexible enough to identify it as an unwanted guest in a changing context. The solution is that the host and the parasite are woven in a contextual and ongoing web of signs constituting mutual recognition on a moment-to-moment basis. In the case of death, for instance, the decomposition of the corpse is mediated by the proliferation of microorganisms living in the gastrointestinal tract. Their violent transformation is a result of a changing context in the most concrete, albeit semiotic, sense of the term. When the host stops functioning as the comfortable guest house that it has been, signs of decay turn the peaceful guests into violent agents. In sum, the polysemy of the sign is an optimal solution to the emergence of complex non-mechanical interactions in and between organisms at different scales of analysis. In this context, meaning making may be defined as "a process that yields the system's differentiated response to an indeterminate signal" (Neuman, 2008, p. 138). Whenever a biological signal is interpreted in at least two different ways under different contexts then we see meaning making in action. From this definition of meaning making, we learn that the immune self, or the contextual and dynamic process through which the immune system contributes to the organism's differentiated existence, involves a continuous distributed process of interpretation. The contextual aspect of this activity is elaborated in the following section.

4. Context: Weaving cues

Natural language processing has made some impressive achievements in building algorithms for Word Sense Disambiguation (WSD). What can we learn from this field for better understanding meaning making in the immune system? First, the challenge facing the immune system may be basically in differentiating between two senses of a sign: Self or Non-Self. In this context, the problem should be simpler than the one of disambiguating the meaning of a sign with more than two potential senses. The situation, however, is far more difficult for the immune system as it does not have a predefined dictionary of terms and senses neither an annotated corpus of sentences in which the different senses of a word are identified. The immune system therefore has to rely on natural intelligence and reasoning from contextual cues. The contextual cues are patterns of co-occurring biological signals resembling those that appear in natural language. For instance, if I have to disambiguate the sense of Bass in the following sentence: "I ate a bass in the restaurant", then the words "ate" and "restaurant" present a minimal context for disambiguating "Bass" as a kind of fish. In contrast, in the sentence: "The musician played wonderfully on the bass during a concert given at the jazz club", the words "musician", "concert", and "jazz club" indicate that bass is probably used in the sense of a musical instrument. Again, we cannot totally dismiss even in this context the other meaning of bass. It is possible, theoretically, that the musician was using a bass fish in order to produce sounds of music that amused the audience during a fringe jazz concert. However, reasoning to the best explanation would lead us to believe that this is not the case. The macrophages are precisely such contextual cues. They cannot sense the antigen directly but report the state of body tissues, the presence and effect of infectious agents, and the state of activation of nearby immune agents. The immunological context is therefore the minimal configuration of signaling agents/pathways through which an ambiguous biological agent is identified as either enemy or friend. This is a dynamic network in which signaling/communication "votes" for a decision through the converging perspective of the immune agents: The T cells respond to the antigen through the MHC but cannot respond to the protein's conformation as the B cells do. The macrophages sense the context but cannot respond to the conformation and so on. The disambiguation of the sign is a complex task in which multiple perspectives converge toward a possible solution. This idea calls for a contextual analysis of immune system activity through tools similar to those developed in Machine Learning and Natural Language Processing. What we need is just a way of mapping the different agents involved in an immune response, recording their behavior through the appropriate sensors, and analyzing these numerous interactions in order to identify patterns of behavior. The development of future sensors for recording the activity of the immune agents would turn this science fiction into science in action. Like the advances made in Brain Machine Interface, it seems that the challenges facing immunology are more "technical", surprising as it may seem, rather than theoretical or metaphysical.

5. Back to the immune self

What have we learned from this rather short journey? The first important lesson is the way our cultural schemes frame and direct our understanding. Imagining the immune self in terms of some Protestant agency has no benefits for understanding the immune system. By presenting this critique, I have no religious critique, á la Dawkins, whatsoever. However, imagining the immune self as a Christian self seems to me a wrong conceptualization even for the devoted believer. As with any other living system that is deeply involved in self regulation, the immune system must have a representation of the "self". As we have learned from cybernetics, there is no regulation without a model. This model must involve a representation both of the requested values the system strives to maintain and those values the system should definitely avoid. However, the immune system, as a complex natural system, is different from the man-made thermostat. Its model of the self is complex, fuzzy, and dynamic, the same as the complementary notion of the "non-self". The immune self is our reified way to describe the processes through which the immune system maintains the differentiated identity of the organism and itself. This is an interpretative process, and to study it in a scientifically productive way we should merge a long hermeneutical tradition asking questions about the nature of interpretation, together with modern understanding of the immune system, future technologies for sensing the system, advanced computational tools for analyzing the sensors' data. These together with good common sense may keep us targeted on the real nature of the immune system rather than going astray after our reified fantasies of the nature of our own selfhood.

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