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Author's Response

Further Reflections on the Language of Immunology

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> Abstract • The composition of living systems is subject to constant change. This suggests a focus on processes rather than entities. So, if questioning the rigid ontological foundations of immunology leads to the question of whether another immunology is possible, a possible candidate is "process immunology." In the target article, I claimed that antibodies are constructed, but I am also open to the view that immunoglobulins are formed by the same naming process. Furthermore, I point out that the problem with "oral tolerance" is that it implies a stimulus-response-regulatory framework. I also draw attention to the "epistemological trap of language," as it is relevant for the public understanding of vaccination. Finally, I discuss the theoretical and practical consequences of accepting Maturana's or Varela's position in explaining the immune system, including the question of whether the activity of our immune system has any influence on our behavior and thus influences our inter-personal world. I conclude by emphasizing that Maturana's biology of cognition and language is not mechanistic because it points to realities "in parentheses" that emerge in the history of human observers.

« 1 » Immunology was, is presently and will remain a special branch of medicine linked to the diagnostic (serological tests), prevention (vaccines), treatment (serum therapy) and other important procedures (blood transfusions, tissue and organ transplantation, cancer therapy, etc.). However, due to the nature of immunological activity, it may be extremely important, also, for basic biology and the understanding of living systems. The big unsolved question remains the nature of living systems as dynamic entities that restlessly undergo structural changes without changing until they change into something else, and die. Thus, in addition to

accepting the unspeakable complexity of living systems, we also have to accept that their composition is constantly in a process of change. This may be difficult to grasp, as we usually distinguish stable entities and regard processes simply as the means of generating such entities.

« 2 » For attending to process rather than entities, the biology of the vertebrate immune system becomes an invaluable research model. Most of my text circles around questions of how and why I claim that antibodies are "socially constructed" (see Chapter 1 "Why ask what?" in Hacking 1999).

« 3 » When Niels Jerne detected an immense variety of spontaneously formed "natural antibodies" (Jerne 1951), he transferred attention away from the mystery of how foreign materials are recognized as antigens onto the developmental biology of the vertebrate organism, and from that developed his selective theory of antibody formation (Jerne 1955). The question to be asked is how are these "natural antibodies" formed? This is a question for developmental biology. In traditional immunology, the organism is merely the place or dimension in which immune responses take place, but a connection with developmental biology adds both a new layer of complexity and an opportunity for deeper understanding (Lonyai et al. 2008).

« 4 » Thus, what **Vitor Pordeus** (§2) says about a paradigm modification may well be justified, because the whole edifice of immunology is based on a metaphor of specificity that is, from my perspective, only (very) partially correct. Making a separation between the immune system and the organism to which it belongs generates the possibility of autoimmune diseases as episodes of faulty recognition and precludes the possibility of defects in the organism itself as the primary event. However, one of the most common human autoimmune diseases, type-1 diabetes, may derive from congenital defective expression patterns in Hox11, which is expressed in embryonic cells destined for the pancreas, salivary glands, tongue, cranial nerves and cochlea (Lonyai et al. 2008). This turns type-1 diabetes into a birth defect, with the commitment of lymphocytes in damage to the pancreas as a secondary development. Developmental biology, or eco-evo-devo, in contemporary terms, is essential to the understanding of immunological activity and to conceive of limits or boundaries for an entity we visualize as the immune system.

« 5 » To answer **Roger Booth**'s (§4) question, already succinctly stated in the title of his commentary, "What Components Contribute to the Immune System?" would require the placement of boundaries around specified regions or components within the entirety of the living system. Given that our naming of the immune system is based on specific behaviors that we find relevant to our lives, there is no clear boundary relating to which components are indirectly entailed yet necessary for the behaviors that we distinguish as the immune response. Furthermore, as I understand it, his question also implicitly asks that the immune system be conceived of as a cognitive system, which, in turn, would require one to explain and understand it in cognitive terms according to how we understand cognitive phenomena (Maturana 2009: 296). Conceiving of the immune system as a cognitive system implies similarities between the immune and nervous systems as relational systems that allow and maintain the adaptation of the organism to its medium. However, neither Humberto Maturana (2017), nor I, or my co-authors cited in the references, see the immune system as a cognitive system.

« 6 » **Alexander Kravchenko** notes that the problem I have distinguished in immunology (observer-dependency) is a general problem in scientific enterprises, because we are all entrapped in the "epistemological trap of language" (Kravchenko 2016). I agree. This trap is particularly dangerous, as it relates to public and official understanding of artificially induced immunity by vaccination, an issue that acquired overwhelming urgency in Covid-19 and may be even more pressing in possible future pandemics. Vaccines are seen as biochemical commands to which the organism passively obeys. This is misleading from a biological standpoint, as I discussed in my target article. However, it is also dangerous in political terms, because individual immunity may be and generally is influenced by vaccination, but an individual response is not determined by the vaccine. Each individual organism changes according to its own history according to its prior path of structurally determined changes.

« 7 » I agree with **Bartlomiej Swiatczak**'s (§1) claim that both antibodies and immunoglobulins arise in the same naming process. Specific antibody formation is simply an expansion of the production of particular forms of gamma-globulin (Talmage 1959) and "the difference between antibodies and gamma globulins exist only in the mind of the immunologist" (Jerne, in Söderqvist 2003: 185). If we agree with Maturana's (2000: 459) general observation that the distinctions we make arise through explaining our experiences with the coherences of our experiences it becomes clear that antibodies are distinguished to coherently explain our experiences. And, in that sense, they exist only in the minds of immunologists.

« 8 » **Luiz Andrade** is very familiar with my previous work and places three meaningful, but very general questions. Answers to these questions are difficult to summarize and discussing their relevance could be extended in future texts. In his Q1, he asks why I disqualify the terminology, oral tolerance, repeatedly used in my academic productions, and why did I not produce another to replace it. The problem is that the expression "oral tolerance" implies "tolerance" as non-responsiveness, i.e., it implicates the stimulus-response-regulation-framework that I avoid. A proper understanding of the phenomenon referred to as "oral tolerance" implies a negation of the traditional way of defining immune responsiveness. Likewise, proposing an alternative designation – such as assimilation, or incorporation (Parnes 2004), also implies a description of a wholesome immunology that entails its own physiology. Providing that description would require more space than allowed here.

« 9 » **Andrade** Q2 also wonders about the theoretical-practical consequences of accepting Maturana's or Varela's position in the description of the immune system. Tracing the differences between Francisco Varela's and Maturana's approach to cognition is a sensitive issue, which became very visible in the two independent prefaces (Maturana 2011; Varela 2011) they wrote for the book *De maquinas y seres vivos*, which they had co-authored together 20 years earlier. However, yes, ascribing cognition to the immune network, or to the immunologist describing them, would have theoretical-practical consequences. The former will search for better methods of analyzing networks; the latter will be concerned with changing general

ways of seeing and possibly devising other methods, perhaps exploring more closely the effects of food antigens and the native microbiota in immunological activity, a concern that never interested Varela (Vaz 2011).

« 10 » Since I am in effect questioning the ontological basis under which immunologists work, Andrade Q3 asks whether another immunology is possible and even whether another science is possible. This a question discussed by Léna Soler (2015) in a debate about "contingentists versus inevitabilists," a distinction introduced by Ian Hacking (1999). Andrew Pickering (2015: 117) asks: "What are we thinking of when we imagine 'a project akin to science' or 'anything like physics'? How can we imagine the space of possibilities? What's in and what's out?" He goes on to state:

> "Growing up, at least in the mainstream of the modern West, is thus an intensive indoctrination in the ontology I just mentioned, that the world has a fixed reliable structure and we can know it: atoms and molecules, quarks and DNA, and so on. And that ontology then serves to underpin our inevitablism – it makes inevitablism inevitable." (ibid: 118)

« 11 » The creation of another, historical-systemic immunology is certainly possible, for example, as a "processual immunology," part of a general movement described by Daniel Nicholson and John Dupré (2018) as a processual metaphysics. There is already plenty of experimental work on describing and analyzing the significance of robustly conserved patterns of immunological activity. This was started by the Stratis Avrameas group, using Elisa plates coated with several different antigens (Mirilas et al. 1999), and it evolved to a modified form of immunoblotting (Nóbrega et al. 1993) in Antonio Coutinho's group. The approach was further developed in several other directions by Irun Cohen's group working with microarrays of proteins inserted by a robotic arm in a glass slide (Cohen 2013). However, all this is still far from becoming a central issue. In short, there are good reasons to believe that if a new immunology emerges, it will be dedicated to patterns.

« 12 » The plurality of simultaneous events taking place in the immune system is immensely complex and cannot be represented in images. Although this complexity is perfectly conceivable in cellular/molecular terms, the concepts that guide research in immunology are still univocal, reactions on a one-to-one basis, and hence remain a dimensional of thousands of concomitant interactions. For example, the notion of T cell "surveillance," i.e., T cell receptors (TCR) detecting small abnormalities such as those in emergent malignant cells, is univocal and there is only one way to interpret it. Nevertheless, this is the metaphor that currently guides extensive experimental research in contemporary cancer immunology.

« 13 » Booth (§4) asks what components of our physiology act as part of the immune network, and, more specifically, whether our nerves and symbiotic microorganisms and their products are part of the immune network. This question devolves to asking whether the activity of our immune system has any influence on our behavior and thus influences our interpersonal world. Though that may seem unlikely, I can refer to Maturana's explanation of emotions as both "relational domains" and as "states of the body" according to the domain in which we distinguish them. We know that emotions entail molecular dynamics that are related to how we act. This is also the case with the network of molecular dynamics from which we abstract the specific dynamics of the immune system. For example, the molecular mediators of neuron activation can act on lymphocytes and cytokines, such as IL-1, which, in turn, can function as a mediator in the nervous system. Consequently, from a functional point of view, there are no clear limits between the immune and the nervous system, and changes in the immune system can indeed lead to changes in our interpersonal world, with the cautionary statement that these are not deterministic changes; they also are contingent on many other aspects of the totality of the autopoietic system.

« 14 » A further example of interconnected influences within the totality is MHC genetics,[1] which can influence sexual selection in mice and possibly also in humans. Though most research has focused on the role of MHC in antigen production, Robert Ader and Nicholas Cohen (1991) have also demonstrated that MHC has an influence on behavioral (or classical "Pavlovian") conditioning of immune responses. Further, we have shown that specific immunization can mediate flavor aversion in mice (Cara, Conde & Vaz 1994, 1997) and this has been shown to involve specific areas in the brain (Basso, de Sa-Rocha & Palermo-Neto 2001).

« 15 » Further to my responses to the individual authors of the open peer commentaries, I would like to add some thoughts that reflection on these commentaries has triggered for me. In 1969, in New York, in the laboratory of Michel Rabinovitch (1970), I saw acanthamoebas exposed to a mixture of sheep and horse red blood cells, clearly choosing sheep red blood cells, as if they had decided to do so. In the text I wrote with Varela in 1978, the source of immunological recognition ceased to be dismembered in lymphocyte clones and became embodied in Jerne's idiotypic network (Vaz & Varela 1978; Jerne 1974).

« 16 » As an analogy to these two perspectives, we might ask whether an amoeba actively seeks food in the environment in which it operates or does it blindly move around as its structure dictates and then occasionally collide with materials for which it has receptors on the membrane, pick them up and ingest them? Does it feed because it moves or does it move in order to feed? If we explain that it moves in order to feed, we implicitly put a small mind in the amoeba, opaque but mental. If it is inadvertently simply colliding with food, we adopt a mechanistic explanation. In immunology, thinking gets confused between these two options. Once again, I will turn to Maturana for an approach to reconciling these two forms of explanation. In the preface to the second edition of *De Máquinas y Seres Vivos*, 20 years after its initial publication, Maturana wrote:

> "[T]alking about living beings as self-referring systems was not satisfactory to me because the notion of 'self-reference' subordinates the dynamics of the components of a system to the totality that results from their operation, which was the very thing that I wanted to avoid when I talked about the local relations of the components of a living being, showing that the living being in its existence

1| The Major Histocompatibility Complex (MHC) of genes consists of a linked set of genetic loci encoding many of the proteins involved in antigen presentation to T cells.

as a totality was a spontaneous result of that manner of operation." (Maturana 2011: 297)

« 17 » Similarly, I conclude that trying to explain the dynamics of any element of the immune system through applying either a mechanistic or a cognitive metaphor are dimensionally incomplete descriptions of a densely integrated totality. It is not just our choice of the metaphors that we use to describe specific interactions (as in the defensive nature of the immune system), it is also our predilection to isolate elements in our desire for comprehensible explanations.

« 18 » I would like to end by emphasizing that the idiotypic network, or more generally an immune system that encompasses more than just that network, arises as a concept relevant to humans, living in language, through what immunologists experientially do and discuss. Taking Maturana's biology of cognition and language into account is an attempt to abandon mental, transcendental concepts. However, because it accepts that we live according to the different realities "in parentheses" (i.e., lived worlds that emerge in the history of human observers), it also encompasses the mechanistic explanations that we generate in those realities.

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