immunology to take the necessary switch from the functional to structural paradigm, and in projecting the scope of this change to deep experimental and conceptual aspects of the immunology.

Jorge Mpodozis Marin holds a PhD in physiology and neurobiology from the University of Chile. He is part of the Council of the Faculty of Sciences, University of Chile, where he teaches regular courses on evolution, neuroethology, and biology of cognition. Jorge is a founding member of the Chilean Society of Evolutionary Biology and the Chilean Society of Neurosciences. He has directed numerous research projects, undergraduate and graduate students, focusing mainly on the anatomy and comparative physiology of the visual system in vertebrates.

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Diseases: Loss of Inner Harmonies?

Humberto R. Maturana
Escuela Matriztica de Santiago, Chile
hmr/at/matriztica.org

> Upshot • An organism is a harmonious closed network of molecular and cellular interactions that produce molecular and cellular transformations and replacements in the continuous realization of its molecular autopoiesis. The processes that we call immunity are dynamics of recovery of that harmony when it is lost as a result of the appearance or intrusion of molecules that do not normally pertain to it, which destroy that harmony, giving rise to what is lived as a disease.

« 1 » In my writings, I refer to cognition, saying that when one says that a person or a system knows, what one is saying is that in her opinion that person or system is behaving or operating in an adequate manner according to the circumstance in which one is observing it. When one says that one knows that something is the case, and one is asked, how do you know? The answer that one gives is always a description of the doings that have to be performed for that to happen. It is in that sense that the metaphor "every living system as it lives operates as a cognitive system" is both adequate and misleading. When I said that in the book *The Tree of Knowledge* (Maturana & Varela 1987), I was claiming that knowing is adequate doing according to what the observer thinks is adequate doing in the circumstances of her observation. But metaphors are generally misleading because they mostly obscure the actual processes that the person who uses them wants to evoke, and in this sense the authors of this article are right.

« 2 » I do not consider it adequate to talk about any system as a cognitive system as a metaphor aiming to evoke how it operates. Systems do not exist by themselves as such. When one talks of a system, one wants to refer to a configuration of relations that one abstracts in the flow of interactions and transformations of a collection of elements that one distinguishes in one's daily living: a configuration of relations that we, as observers, distinguish as spontaneously or artificially being conserved in some domain of our concern. A tornado, for example, is not an entity with definite borders, and extends only as far as the observer chooses what must be conserved in its dynamic. The same happens with what is called the immune system, which does not exist by itself, and appears only when we, as observers, distinguish in an organism a configuration of dynamic relations that we think must be conserved in it, so that what we call immune processes appear.

« 3 » An organism exists (regardless of whether it is unicellular or multi-cellular) as a closed network of cellular and molecular processes in which molecules and cells produce and destroy one another in a harmonious manner that continuously results in the organism's self-production through the realization of its molecular autopoiesis. In this process, molecules enter and come out of the organism while the organism remains in its dynamic closure, oblivious to what we, as observers, see as its ecological niche or environment. In the evolutionary history of the different kinds of organism that constitute the biosphere, the different kinds of molecules appearing inside them, either being produced by them or entering into them from the medium that contains them, have fundamentally five different destinies independently of where they come from. They may…

- be incorporated in the normal metabolic processes;
- be destroyed;
- disharmonize the normal metabolic processes;
- be expelled; or
- accumulate in the organism.

« 4 » The manners of dealing with the molecules that appear inside the different kinds of organisms currently living have been transformed and changed along the natural drift of their respective lineages according to the manners of living that have been conserved in them (Maturana 1980; Maturana & Mpodozis 2000). Natural drift is not a history of adaption to a changing medium but a history of conservation of the realization of living of the organism in a transforming and changing ecological niche that does not preexist as such, but arises as it slides in the medium in the tangent of the realization of its living. Therefore, to understand what we obscure by talking of "immune systems" we have to look at what harmonious networks of normal processes of molecular and cellular productions and interactions are conserved by the destruction of the molecules or cells that disrupt them. I cannot answer these questions because I do not study these processes. Yet I feel that when we attend much to what we think is the description of the function of a process with respect to the operation of the organism in its niche, we do not fully see how that process occurs in relation to the realization of its living.

« 5 » In the process of realization of the molecular autopoiesis of an organism there is no "concern" with the environment in which it operates, so there is nothing in the inner operation of the organism other than harmonious metabolic processes that conserve its living, or it dies. Similarly, in the inner dynamics of the operation of the nervous system of an organism there are only changes of configurations of relations of neuronal activities that are adequate for the conservation of its living in the tangent of the historical present in which the organism realizes its molecular autopoiesis, or not and becomes ill and recovers … or does not recover and dies. If we confuse our description of the immune processes thinking in an

immune system with what actually happens in the network of the molecular processes that conserve the harmonic metabolism of a healthy organism, we do not understand one or the other.

« 6 » In my opinion the constellation of the phenomena of immunity, self-immunity, and oral tolerance that we deal with in mammals shows that they are aspects of the historical transformation and conservation of the harmonious network of processes that realize the molecular autopoiesis of organisms that are members of lineages of changing manners of living in a changing ecological-niche. In this niche there are always different kinds of external molecules appearing that penetrate them, some of which interfere with their normally harmonious metabolism of self-production. Taking this perspective, it is thus important to understand the interrelated networks of cellular and molecular productions and transformations of the continuous realization of the organism in its continuous realization of its molecular autopoiesis as a single system, rather than viewing these different networks as different organic or metabolic systems that satisfy different functions. I cannot embark on this project, at the moment, but I think that in their target article, Nelson Vaz and Luiz Andrade are on the right track to do so. Yet, I and my colleague Ximena Dávila are working on the understanding of dynamic "ecological organism-niche unity" in that every organism integrates in the realization of its molecular-autopoiesis (Maturana & Dávila 2015).

Humberto Maturana Romesín was interested in animals and plants from childhood and wanted to be a biologist to investigate life that dies. A long period of reflection, reading Friedrich Nietzsche and Julian Huxley, occurred during three years of complete bed rest. Beginning medicine in 1950, in 1958 he received a PhD in biology from Harvard University. He is presently working in the "Escuela Matríztica" in Santiago, Chile, with his colleague Ximena Dávila Yáñez, in the domain of cultural-biology, and together they have published the book *El Árbol del Vivir* (2015).

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Self and Non-Sense: The Radicality of Varela's Contribution to Immunology

John Stewart
Université de Compiègne, France
js4a271/at/gmail.com

> Upshot • The commentator's motivation for accompanying Varela in a foray into immunology lay in the clear-cut, value-laden contrast between traditional immunology and the new organism-centred view pioneered by Vaz and Coutinho. In the twenty years that have elapsed, models have become increasingly complicated so that this clear-cut contrast has been obscured. In immunology as in cognitive science, the radicality of Varela's views is disturbing for the mainstream community.

« 7 » When Francisco Varela and I made our foray into immunology (Stewart, Varela & Coutinho 1989), the situation seemed clear: there was a stark contrast between "traditional" immunology and the "organism-centred" view being developed by Nelson Vaz, Antonio Coutinho and other immunologists (Coutinho et al. 1984). It is generally agreed that the repertoire of immunoglobulins is "complete"; the variety of immunoglobulins is such that there is at least one (and probably more) immunoglobulin that will interact with any organic macro-molecule of sufficient size. In cognitive terms, this means that the immune system "sees everything." The difference between the two paradigms lies in the consequences of this. On the traditional view, the immune system basically destroys everything that it sees; this is coherent with the view that the primary function of the immune system (as the very term "immune" implies) is to defend the organism against potentially pathogenic invasions from outside. On the organism-centred view, the consequence of the fact that the repertoire is complete is that the "immune" system will first and foremost perceive *itself*. The formation of an "idiotypic" network will be practically inevitable, and this will be at the heart of the *constitution* of a molecular identity and "self."

« 8 » The contrast between these two views is heightened if we address the question of the relation between the "immune"[1] system, and the organism that houses the system, i.e., the "self" in a common-sense use of the term. On the traditional view, if one admits that the immune system destroys everything that it sees, the immediate prediction is that the immune system should destroy the organism that houses it. Of course, this cannot happen, so one is forced to a rather uncomfortable *ad hoc* adjustment: the immune system sees everything *except* the "self." Philosophically, this is exactly wrong: what a system perceives is, *ipso facto*, the self – and this is indeed at the core of the "organism-centred" theories associated with the concept of autopoïesis.

« 9 » Moving on from these theoretical and conceptual issues to empirical data, what we have said means that the opposition between traditional and organism-centred views will focus largely on the phenomenon of auto-immunity: although the immune system never totally destroys the body that houses it, there are numerous clinical cases in which the immune system does indeed cause inflammation and damage to a part of the organism. On the traditional view, auto-immunity arises because the immune system is doing *too much*, and so clinical treatment will consist of *immuno-suppression* (largely by drugs). By contrast, on the organism-centred view, auto-immunity arises because the immune system is not doing enough, and so clinical treatment will consist of *stimulating* the immune system (in particular the idiotypic network) in appropriate fashion. Such treatment does not necessarily require pharmaceutical drugs; the work of Nelson Vaz on oral tolerance, which he refers to in his text, illustrates this nicely.

« 10 » It was this clear-cut contrast between the "traditional" view, and the organism-centred view that challenged it, that was my prime motivation when I accompanied Varela in our "foray" into immunology (nei-

1 | The inverted commas around "immune," here and elsewhere, indicate that attributing a primary role of destroying foreign invaders is not an absolute necessity; it certainly characterizes the traditional view, but is not necessarily taken over by alternative views.