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

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> 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.

ther of us was a "professional" immunologist). To bring out the value-laden nature of this opposition, I may note that the traditional view is based on a military metaphor: "seek and destroy." By contrast, the organism-centred view has at its core the philosophical principle of *gnothi seauton*, "know thyself," which I find intrinsically much more satisfying.

« 11 » Varela's contribution to immunology, recounted here, was made over 20 years ago. What has happened since? My own perception is that the main development has been that models have become increasingly complicated, involving multiple interactions between B lymphocytes and several classes of T lymphocytes. The result has been that the clear contrast between two alternative views, which as I said is what attracted me to work in immunology, has been largely obscured. In my view, this amounts to "missing the woods for the trees."

« 12 » Varela's concept of enaction, in its original radical form, applies to each and every one of us, every minute of every day of our life. And this means that each of us is personally responsible for "bringing forth" our own particular world of lived experience. I propose to call this "existential enaction," and it is intensely value-laden and subjective. Now this poses a problem to normal scientists, because science is supposed to be "objective" and the usual route to objectivity is to eliminate everything subjective. This can indeed be done; it gives rise to what I propose to call "4E enactivism," where cognition is seen as embodied, embedded, extended and only incidentally as "enacted" (without saying what that means). 4E enactivism is currently popular, which is understandable because it enables scientists to return to the comfort zone of excluding their own subjectivity, but I consider that this amounts to fatally watering down existential enaction, and thus "missing the woods for the trees."

« 13 » I would like to conclude by remarking that there seems to be a pattern here. We now have two examples where Varela's conceptions, disturbingly radical, have been watered down so as to return to normal science. Might it be that the heart of Varela's contribution to science has been to systematically challenge us, to interrogate our subjectivity as scientists?

John Stewart, born in 1941, was educated at Cambridge, England. After an initial degree in Physics, and a PhD in genetics, he has subsequently lived in France, worked at the CNRS in a variety of fields: notably the sociology of science and, more recently, cognitive science and the paradigm of enaction. He is currently writing a book aimed at re-establishing living organisms as such as the central object of biology, rather than the gene-centred focus on DNA that is dominant in contemporary molecular biology.

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Francisco Varela and Immune System Modeling, Closure, Cognition and Enaction

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> Upshot • Vaz and Andrade recount how Varela collaborated with a group of immunologists to advance a nonconformist view of the immune system. Here, I outline my interpretation of four concepts related to the philosophy of the immune system that Vaz and Andrade associate with the ideas of Varela: modeling, cognition, closure and enaction.

The Jerne-Vaz-Varela insurgency

« 1 » In §11 of their target article, Nelson Monteiro Vaz and Luiz Antonio Botelho Andrade contrast the mainstream antigen-centered clonal selection theory (CST) model of Macfarlane Burnet (Figure 1A) with the organism-centered, idiotypic network model of the immune system developed by Niels Jerne (Figure 1B). Basically, the CST of Burnet sees the immune system as a collection of independent antibodies and immune cells – lymphocytes – each bearing a unique receptor for an antigen. The definitions of antigens, antibodies and lymphocytes are circular but useful: an antigen is any molecular shape that can be bound by the combining site of an antigen receptor or by an antibody; an antigen receptor or an antibody is a molecular structure that can bind to an antigen in a way that triggers an immune reaction – the lymphocyte or antibody that "recognizes" the antigen is activated to neutralize or destroy the antigen or the cell, bacterium or virus that bears the antigen.

« 2 » The classical CST model postulates an important limitation to the world of antigens: Only antigens foreign to the body are normally recognized by lymphocytes or antibodies; the healthy immune system is blind to the body itself (Cohen 1994) because any antigen receptors that might be able to recognize the body's own molecules (self-antigens) are purged from the immune system early in development. The normal, healthy immune system cannot recognize self-antigens and so immune reactions cannot be directed to the self. In other words, the CST model represents the immune system as the arbitrator between the foreign and the self – the foreign is rejected and the self is tolerated blindly. The goal of clonal selection is *defense* – the immune system has evolved to seek out and destroy all foreign molecules or cells that might threaten the integrity or health of the body.

« 3 » Jerne proposes a different view (§11, Figure 1B): the lymphocytes and antibodies of the immune system are not independent agents waiting to activated by a specific foreign antigen, but rather are interdependent entities that are in constant interaction with one another; the structure of an antigen receptor acts like an antigen for some other antigen receptor – the immune system, in short, is a network of immune agents in continuous interaction with the antibodies and antigen receptors of the other agents in the system. This network is in balanced equilibrium – it is in a state of tolerance – until it is perturbed by an antigen that enters the system and interferes with the connectivity of the network; the perturbation occurs when the intruding antigen happens to bear a molecular structure that mimics the structure of an antigen receptor or an antibody connected within the network; the intruding antigen interferes with receptor-receptor interconnections. This antigen interference upsets network equilibrium, ultimately resulting in an immune reaction. Francisco Varela was attracted to Jerne's immune system network of internal connectivity and collaborated with members of the Paris group organized around Antonio Coutinho, as described by Vaz and Andrade in §14 and §18.