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.

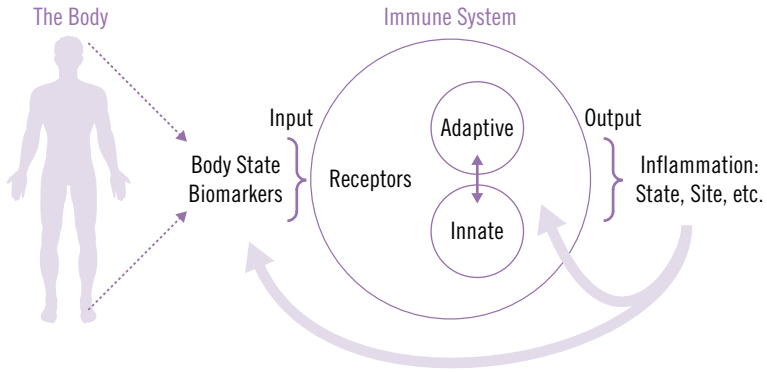


**Figure 1 •** An updated picture of immune-body networks – the immune system computes the state of the body and learns from the experience. The input to the immune system is composed of biomarker molecules reflecting the state of the body; adaptive and innate immune receptors receive the input and activate networks of immune cells and molecules to process the input information; the output is appropriate inflammation that feeds back to modify the state of the body and the structure of the immune system.

« 4 » Jerne's internally connected immune network model was attractive to the Paris group because it appeared to solve three problems unresolved by Burnet's CST of independent clones: regulation of autoimmunity to self molecules; immune tolerance; and immune pathology. Contradicting Burnet's assertion, healthy immune systems were experimentally demonstrated to be replete with receptors and antibodies that could bind to self-antigens (§26, Cohen 2000b). Immune self-recognition is a fact, but self-recognition does not usually lead to autoimmune disease; autoimmune disease is prevented by internal network connections. Moreover, even foreign antigens – present in the food we ingest (§22) and the air we breathe – can be tolerated (not attacked) by internal network connections. Finally, pathogenic autoimmunity and damaging inflammation could be attributed to clones of lymphocytes that have undergone abnormal proliferation (§36) and so have broken loose from regulatory network connectivity.

« 5 » The target article by Vaz and Andrade concludes with two points summarizing Varela's position (§38):

a Varela sees the immune system as a cognitive system, and

b the network connectivity of immune cells is responsible for immune tolerance.

Vaz and Andrade disagree with the first point – in their view, the immune system is not cognitive. However, they do agree with the second point – that universal immune-cell connectivity favors tolerance. In several sections (§9 and §12), Vaz and Andrade discuss Varela's interest in *closure* – the idea that the immune system is a closed entity that emerges from the interconnected networks of lymphocytes and antibodies proposed by Jerne.

## The immune system-body networks

« 6 » Before we discuss the concepts of immune cognition, tolerance, closure and enaction, I would like to present an updated picture of immune networks (Figure 1): We now know that immune cells and molecules are not only connected amongst themselves in an immune network; elements of the immune network exist in continuous interaction with the body. In other words, dynamic changes in the state of the body – local or widespread – are sensed by the immune system, locally or generally. If we define computation[1] (in the sense of Turing) as the translation according to rules of input into output, then we can say that the immune system computes the state of the body (Cohen 2007).

« 7 » Computation poses questions: what is the input from the body to the immune system to be computed; what is the computational output of the immune system; where does the immune output go and who reads it?

## Body-immune input

« 8 » The immune system receives *input* from the body in the form of *biomarker* molecules (Cohen 2013). The particular biomarkers and their concentrations and dynamics express the *states of body tissues,* which the immune system perceives by way of its various receptors – adaptive receptors for antigens along with innate receptors for cytokines, chemokines, adhesion molecules and many other molecular signals (Figure 1). The body states sensed by the immune system include healthy cell growth and development, aging, metabolic activity, energy transactions, traumas, infections, malfunctions, genetic aberrations and cancer – all sorted anatomically by local lymph drainage into regional lymph nodes and other types of lymphoid organs. The types and amounts of information that flow from the body to the immune system are sensed by the receptors of immune cells and molecules and integrated dynamically by network interactions between the immune cells and their molecular products.

## Immune system processing

« 9 » Figure 1 depicts the immune system composed of mutually interacting *adaptive* and *innate* networks. Adaptive immunity refers to lymphocytes, which undergo somatic differentiation to express receptors for antigens, and so adaptive lymphocytes recognize antigens and some lymphocytes secrete their antigen receptors as antibodies; innate immune cells do not bear antigen receptors and do not recognize antigens, but they are critical to immune inflammatory processes (Cohen 2000b). All the cells of the immune system, adaptive and innate, receive biomarker input signals from the body. These body signals are modified, amplified and abated respectively by various immune cells according to the ex-

1| Note that I use the terms *computation* and *compute* strictly as I have defined them here – the transformation of input information into output information; computation in this restricted sense should not be confused with any computational theory of mind.

isting state of the cell, the immune system as a whole and its past history – the immune system learns from its lived experience.

« 10 » Adaptive lymphocytes and innate immune cells are connected functionally by interaction molecules such as cytokines, chemokines and others. My colleagues and I studied the network architectures of immune and body cells interconnected only by cytokines, which we culled from the literature in 2006 (Frankenstein, Alon & Cohen 2006); these networks were formed by 29 different cytokines connecting 16 types of immune system cells, both innate and adaptive, and 15 types of body cells. If we were to repeat the study today, we would arrive at considerably greater network complexity. Thus, the immune system is actually an extended network of many types of cells, antibodies and other molecules.

« 11 » The biomarker input from the body is transformed by the responding immune cells and molecules into internal immune signals, which are transmitted and modified by the interconnections of the immune cells – similar to the way sensory input into the brain is transcribed into brain network signals. Computations of body state by the immune and nervous systems are tuned to different aspects of living, but both systems process their input information by transforming it into network interactions internal to the system. Internal processing leads to effector outputs.

## Immune-body output

« 12 » The outputs of immune information processing generate various types of immune reactions, which include the activations, proliferations and migrations of immune cells to various body sites, particularly to abnormal tissues. These immune reactions are reflected in what is termed *inflammation*. The effects of inflammation depend on the tissue context and the type of inflammatory reaction: on the one hand, inflammation can heal wounds and broken bones, produce scar tissue, activate blood vessel formation and tissue regeneration, modify metabolism, and even advance the implantation of the developing embryo into the wall of the mother's uterus (Dekel et al. 2014); on the other hand, inflammation can destroy infected, aged or cancerous body cells, and neutralize pathogens. Immune inflammation is even essential to maintain our healthy microbiota (Swiatczak & Cohen 2015).

« 13 » Inflammation is a dynamic process that must continuously adjust itself to the changing biomarker signals that mark the healing response; immune computation is a dynamically varying process. Unfortunately, however, inflammation also has the power to harm; the same processes that heal can cause disease if they are poorly regulated, excessive, misdirected to the wrong site, unnecessary, or chronically persistent or intermittently repetitive. Biologic computation, immune and nervous, is a delicate matter.

## Immune-body and immune-immune feedback

« 14 » The inflammatory responses generated by the immune system dynamically mediate two feedback effects:

- they modify the states of the body, as we have discussed above, and
- they modify the organizational structure of the immune system itself.

In other words, both the body and the immune system react to each other to change both the targeted body tissues and the immune system itself; Figure 1 shows two feedback arrows. The immune system, like the brain, exploits experience to develop competencies far beyond its inherited genetic endowment. In essence, the immune system computes the state of body tissues and translates tissue needs into inflammatory responses appropriate for maintenance, healing and defense.

« 15 » Now we can return to Francisco Varela and to the points raised by Vaz and Andrade.

## Immune system closure

« 16 » In §9, Vaz and Andrade report Varela's concern that Jerne's idiotypic network is not a formally closed system in the sense of being a *self-sufficient entity*. Comparing Figure 1 in Vaz and Andrade with my Figure 1 here, it is clear that *closure* does not apply to the immune system as I have described it. Closure, nevertheless, is a clarifying concept: the lack of closure underlines the fact that the immune system does not exist as a system outside of its ongoing interaction with the body; the immune system has no *self-sufficient entityness,* its existence is contingent. I would hazard to say that no biologic system exhibits closure; living systems exist in interaction with their environments. There is no brain in a vat and no immune system in a vat. Life is a web of interacting, interdependent sub-systems.

## Immune cognition

« 17 » Whether the immune system is cognitive or not depends on how you define cognition – In *Tending Adam's Garden: Evolving the Cognitive Immune Self* (Cohen 2000b), I defined a cognitive system as one that learns from experience, one that computes its input to "select" among a range of optional output responses, and one that deploys biomarkers (organized internal images) to carry out its activities. The fact that the immune system makes mistakes and can repair them (autoimmune diseases, for instance), is evidence for cognition.

« 18 » Indeed, the immune system is an ideal subject for cognitive enquiry – the immune system is a model cognitive system, which, unlike the brain, is not cluttered by conscious awareness or intensions. The immune system might conveniently demonstrate how collectives of interacting elements make cognitive, computational decisions. The brain, too, works without its own brain.

## Immune enaction

« 19 » Varela and colleagues introduced the term *enaction* to represent the idea that a cognitive system builds itself through a mutual interaction with its environment – the cognitive system enacts a world (Varela, Thompson & Rosch 1991). The cognitive system does not passively receive information from its environment and then translate the information into pre-formed internal representations; on the contrary, the cognitive system builds itself as a consequence of the actions it performs as it interacts with its world. Varela's *enaction* is an accurate description of the way I see the immune system (see Figure 1).

## Immune tolerance

« 20 » Let me close with a comment about a term mentioned many times in the article by Vaz and Andrade – *tolerance*. Immune tolerance is used by immunologists

generally to indicate "stabilization of immune activity," whether the stabilization is to dietary or microbiota antigens (§29) or to any antigen including self and foreign antigens; tolerized antigens do not evoke an immune effector reaction that activates damaging inflammation. The problem with *tolerance*, as I see it, is that the term implies a reference to its opposite – *intolerance*. The implication is that the immune system has two polar types of behavior: it either tolerates an antigenic entity peacefully, or it attacks and rejects the entity intolerantly; the immune system is normally tolerant to the self and normally intolerant to the foreign. This binary division of the immune world is a misleading carryover from the classic CST paradigm – the natural response of the CST immune system is to defend the body by attack, unless there is some reason for the system to tolerate the situation.

« 21 » *Tolerance*, however, is an anthropomorphic conceit; immune receptors respond only to their ligands, they are neither tolerant nor intolerant – so too an immune receptor does not distinguish between self and not-self, or between danger and not danger (Cohen 2000a, 2000b). Tolerance, intolerance, self, foreign, danger and safety are all ideas of human minds that have been forced onto the immune system. Figure 1 shows us that the immune system merely integrates signals it receives from the body and responds with appropriate types and degrees of inflammation – it computes. Sometimes the output is rest or repair and sometimes the output is reject and destroy – with all intermediate grades of dynamic intensities in-between. The healthy microbiota in the gut do not harm the body and no clinical response is sensed; the same microbes entering the blood can induce immediate death by triggering an intense, system-wide toxic shock reaction; here the bacteria have killed their host by the host's over-exuberant immune reaction. The immune system, in the spirit of Varela, has no preconceived notions – it merely enacts a world.

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## Authors' Response

# Not Objective, Not Subjective – Something Else: Coordination of Actions

Nelson Vaz & Luiz Andrade

**> Upshot** • Mpodozis and Maturana endorsed our way of seeing and enrich the debate, offering their own arguments. Stewart and Cohen criticize some points of our article. Stewart thinks that we are "watering down" Varela's enactivism and approaching objectivism; we show why this is not what we believe. Cohen offers a long (generous) description of his own functional idea of immunological activity and we show why our positions are incommensurable; agreeing with Mpodozis's comment, we claim that nothing is gained by ascribing cognitive properties to immunological activity.

### Endorsing views

« 1 » We agree and fully endorse Jorge Mpodozis's commentary on the importance of prioritizing a structural approach over the functional approach, since the latter is loaded with a veiled form of animism, in reducing the emergent properties of the system (recognition, memory, tolerance, etc.) to its constituent cells (lymphocytes) and molecules (immunoglobulins). This change in ways of seeing is of paramount importance for immunology and medical thinking, which is still strongly tied to the functional approach and to a set of defensive metaphors (Vaz & Carvalho 1993) that give life to this approach. Beyond this, Mpodozis's comments are most valuable to corroborate our way of seeing. He questions the value of ascribing "cognition" to immunological activity, arguing that neither as a phenomenon nor as a mechanism is this notion useful to our understanding of immunological phenomena and mechanisms. In short, he asks whether it is "worth treating the immune system as a cognitive system." He answers negatively, as we have done in the target article and in other publications. In defining "systems," he makes clear that the traditional way of seeing lymphocytes independently undergoing clonal expansions fails to characterize an immune system as usually understood. We also agree with Mpodozis's statement that "the ascription of functions may […] lead to a neglect of relevant structural aspects of the systemic constitution" (§7), as well as with his call for a "necessary switch" of paradigm in immunology.

« 2 » In his recent publications, Humberto Maturana has introduced the notion of "harmony" to describe the physiologic operation of living beings. This may become confusing to those not familiar with his ideas because, for him, living beings are either alive or dead, with no intermediate state. In his preface for the book *Guia Incompleto de Imunobiologia*, one of us, Vaz, wrote with Ana Maria de Faria (Vaz & Faria 1993) that Maturana claims that "(a) Health is a cultural phenomenon, a phenomenon typical of a vision of what is desirable in life. Living beings live and in their living have neither health nor disease"; and (b) that our book "[…] enlarges the view of the organism as a systemic totality: the inner space becomes a closed molecular and cellular relational dynamics, which defines the unity of the organism instead of being defined by it" (Maturana 1993: 5f, our translation). Thus, we assume that Maturana fully understood and agreed with our proposal of "oral tolerance" as a conservative process involved in the creation and maintenance of the vertebrate organism, i.e., as an aspect of its autopoiesis and of the conservation of the adaptation of the immunologic system to the organism. He also understood that our approach to immunology helps to define the organism, instead of defining immunity as something functional (defensive).