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).

Critical views

« 3 » The title chosen by John Stewart for his commentary, "Self and Non-Sense," is an expression that illustrates quite well what we had in mind in Denver, in 1978 (Vaz & Varela 1978). Created by Luiz Carlos S. Maia, a dear friend and close collaborator of mine in the investigation of oral tolerance, the expression acquires special relevance because the present article does not intend to minimize Francisco Varela's contribution, but points to his neglect of oral tolerance, which, in our way of seeing, is of paramount importance in revealing the nature of immunological activity.

« 4 » Stewart (§6) claims that we are offering a second example of "watering down" Varela's enactivism, and we disagree with his interpretation. Vaz (2011b) makes it quite explicit that we are not moving in the direction of "fatally watering down existential enaction," but rather we are expressing our preference for concepts proposed by Maturana's biology of cognition, where the presence of the human observer and his operation in "languaging" is of critical importance. In 1968, Maturana became aware it was perfectly possible to correlate the electrical activity of the retina with the name given to the experienced color (Maturana, Uribe & Frenk 1968). The color we call "green," regardless of its spectral composition, which can vary widely, was associated with defined patterns of retinal activity. This bold step involved the ("languaging") activity of the observer (still called a "beholder" in 1968) in creating the experimental phenomenon, a step taken one year before the development of the notion of autopoiesis. This was important in the subsequent development of his theory on the nature of human cognition and living activities in general (Maturana 1970a, 1970b). We see a parallel between ascribing names to colors and ascribing names to immunoglobulins used as specific antibodies, as noted by David Talmage (1957) and Niels Jerne (1974a, 1974b). Vaz (2011b: 335) argued against the "fallacy of univocality" – the claim of apparent unlimited, unambiguous, detailed molecular precision –, because this fallacy hides the role the immunologist plays as a human observer who interferes in what happens. In this sense, there is a crucial difference between seeing this as "existential enaction" and "subjective," and what Maturana calls "intersubjectivity" generated by human observers operating in "languaging" (Maturana 2002). Therefore, emphasizing the importance of including the observer in her own act of observing and conceiving the object does not mean a return to classical objectivism, but a further step towards understanding certain phenomena and, perhaps, also towards our praxis as reflective scientists, as pointed out by Varela, Evan Thompson and Eleanor Rosch (1991).

« 5 » Despite our sincere admiration for the broad path pioneered by Irun Cohen and his colleagues, who have investigated the complexity of immunological activity in more than five hundred articles, we have two conceptual divergences that are worth emphasizing for a better understanding of what we say in our article in relation to Varela's legacy to immunology. Although the model presented by Cohen in his Figure 1 has some congruency with a conception found in the set of ideas of Maturana and Varela (1980), when these authors emphasize that both the nervous system and the immune system are structurally coupled to the body of which they are parts, Maturana and Varela question the concept of information and the notions derived from it, such as input and output. Regarding the structural coupling of the nervous system to the organism, they state that:

> "The nervous system is a network of interacting neurons coupled in three ways to the organism of which it is the component: (i) The organism, including the nervous system, provides the physical and biochemical environment for the autopoiesis of the neurons as well as for all other cells, and, hence, is a possible source of physical and biochemical perturbations which may alter the properties of the neurons and thus lead to (ii) or (iii); (ii) There are states of the organism (physical and biochemical) which change the state of activity of the nervous system as a whole by acting upon the receptor surfaces of some of its component neurons, and thus lead to (iii); (iii) There are states of the nervous system which change the state of the organism (physical or biochemical) and lead recursively to (i) or (ii)." (Maturana & Varela 1980: 125)

« 6 » It is noted that we can replace neurons by lymphocytes to understand the coupling of the immune system to the organism of which it, as well as the nervous system, is a component. Thus, for the observer, they can be considered as subsystems of a larger system, the organism as a whole. Maturana calls the phylogenetic and ontogenetic history of this process of coupling the different subsystems to the organism: "harmony."

« 7 » From his theoretical approach to more general biological issues, expressed in his books (notably *Tending Adam's Garden*, Cohen 2000b) and books and articles in collaboration with the philosopher Henri Atlan (e.g., Atlan & Cohen 1989), the general outlook stressed is based on the notion of *information*. The questioning of the use of information in biology has already been the subject of a debate between Maturana and Anthony Fedanzo (Maturana 1983). Not to dwell on this discussion about information, we will make a few comments about it before addressing Cohen's main criticism of our article, i.e., that we disagree with Varela's claim about considering the immune system a cognitive system.

« 8 » The term information has two specific and distinct meanings, one quantitative, technological – measurable quantity of bits (binary digit) – coming from classical information theory, developed by Claude Shannon and Warren Weaver in 1949; and another more qualitative, used more broadly, including, but not limited to: models, figures, shapes, configurations, ideas, indexes, images, icons, signs, symbols, signifiers, gestures, positions, contents, intonations, rhythms, words, actions, and silences. This extended sense is given the technical name of "variety" (Wilden 2001). Thus, while information represents a type of coded/decoded variety, noise is a non-coded variety that disrupts information and therefore should be avoided. As a result of this subdivision, certain types of variety will be valued as information, other types remain neutral (data) and others will be rejected as noise. Taking this exposition a little further, we will see that appreciation (interpretation, acceptance and use) depends on the context. Without a context, everything is homogenized and a distinction can no longer be made between information, data and noise. That is, for a totalizing information, it is equivalent to say that it does not say anything, it does not inform anything, it is zero

information, since the context disappears (Wilden 2001).

« 9 » A modern technology-based society uses the term information in several areas of knowledge, especially in communication engineering, where it is assumed that information has the sense of transmitting a message through two or more systems designed and constructed in such a way that they are isomorphic and complementary (originator and receiver). However, the origin and organization of living beings, from the perspective of evolutionary theory and biology of cognition, states that all living beings, including ourselves, are fruits of ontogenetic and phylogenetic stories and, therefore, were not intentionally designed and constructed with complementary "embedded" isomorphic devices that guaranteed a priori language and communication (Maturana 1983). Therefore, from the perspective of biology of cognition, there are no inputs or outputs of information between the environment and living beings and, consequently, information, as a concept or explanatory principle (ibid), is dispensable for the understanding of language, cognition and knowledge (Maturana & Varela 1987).

« 10 » Cohen's model (Figure 1) is more genuinely cognitive than any other model in immunology, but the way he sees cognition is quite different from ours. He ends his §7 asking: "[…] who reads it [i.e., the immune output]?" We answer: the immunologist, the human observer operating in human language. In §17, Cohen says that "whether the immune system is cognitive or not depends on how you define cognition" – in a nutshell, this is the kernel of discrepancies between Cohen's approach and ours. We accept the theoretical framework proposed by Maturana and Varela (1980, 1987), who conceive cognition to be an adequate conduct of an organism in the face of a context, specified by the observer. Following this line of thought, the authors show that cognition can be extended to all living beings, since every living being has, in one way or another, a behavior appropriate to its environment, its ecological niche, and dies when this adequacy, the structural coupling with the medium, gets lost, i.e., it dies when it ceases to know. This has been summarized by the authors' aphorism "to live is to know." It is precisely because only the organism, in its relationship with its environment, can show an adequate conduct, judged by the observer, that we state that the immune system, or the nervous system, is not a cognitive entity. Nevertheless, we agree with Cohen in pointing out that analyzing the immune system may be useful for the understanding of cognition as a biological phenomenon. Paraphrasing Cohen, we could say that the immune system can conveniently demonstrate how collectives of interacting elements, *create phenomena that we, human observers, see and metaphorically describe* as cognitive.

« 11 » Speaking a little bit about tolerance and biological closure, we agree that "tolerance, intolerance, self, foreign, danger and safety are all ideas of human minds that have been forced onto the immune system" (§21). Similarly, the same may be said regarding the notions of information, computation, biomarkers, etc. Everything said is said by an observer to another observer who can be himself or herself" (Maturana 1978: 31). The attitude toward the concept of "closure" is a major point of departure between Cohen's proposal and ideas defended by Jerne (1974b) (e.g., self-sufficiency); Varela's "organisational closure"; and our own notion of "tolerance" as dynamic stability (Verdolin et al. 2001). The idea of "closure" has been difficult to accept even by important network immunologists, including Antonio Coutinho (2003). Closure is not isolation: all systems are open to interactions. Both Varela and Maturana have made this quite clear. To Cohen, however, no biological system exhibits closure. To us, living and non-living systems exhibit "closure" understood as their "organization," i.e., the set of invariant relations (among components) that defines their class-entity (a system exists as long as the relations between its components remain invariant). These entire misunderstandings stem from failing to acknowledge the central notion of "organization" defined as the set of invariant relations (among components) that defines the class-entity of a system (Maturana & Varela 1980, 1987).

Conclusion

« 12 » We maintain our view that the immune system compensates perturbations coming from the organism itself (and from its own operation), which in its turn undergoes perturbation triggered by the medium and by its own activity. These activities are always determined by the organization and structure of the system. Thus conceived, the immune system is capable of learning, because its invariant organization allows for structural changes. It presents memory as one of its emergent properties, not because it presents "memory cells," but because the system as a whole can assume different patterns of activation, which the observer comments on, through its criteria of distinction, as faster, more intense and specific. If these standards and the comments on them have the body as a reference, it follows that cognition, as an emerging property, should not be ascribed to components of the organism, or to local rules, or to their subsystems, but to the organism as a whole, in its interaction with the environment. This view is the result of our experimental work with "oral tolerance" understood as a dynamic stability and robust conservation (Vaz et al. 2003; 2006) of levels of specific responsiveness (Verdolin et al. 2001) and our own praxis as reflective scientists, influenced by long and numerous repeated conversations with Varela and all our commentators.

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