DEMOBILIZING IMMUNOLOGY: AUTOPOIESIS AND AUTONOMY IN FRANCISCO VARELA'S THEORY OF IMMUNITY

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Abstract

This thesis examines the transformative impact of the immune network theory on theoretical immunology, especially how immunity has been understood and described metaphorically in the scholarship. The immune system had been conventionally couched in warfare rhetoric. At the end of the nineteenth century, Russian scientist and pathologist Elie Metchnikoff depicted pathogens as savages in the theory of phagocytosis, which, he postulated, the body must destroy with equal ferocity. Virologist Frank Burnet further affirmed this concept in 1957. In the Clonal Selection Theory, he articulated the model of self and non-self discrimination, thus giving rise to the idea of the immune system as a defense and attack system. In 1979, Francisco Varela and Nelson Vaz proposed that the immune system should be considered instead as a network in "Self and Non-Sense." At the heart of their theory was the notion of self-determination that emphasized the goal of the immune system was to maintain the autonomy and individuality of the organism. This non-martial interpretation was rooted in the theory of autopoiesis, whose conceptualization was greatly influenced by Varela's experiences of the political and social chaos in Chile during the Allende regime and the Pinochet dictatorship. I will explore the extent to which Varela's immune theory was a political critique of the condition of his homeland, and beyond that, the ideological hostility that divided the world between capitalism and communist in the post-1954 era. Further, the importance of the whole of the organism was also reiterated in his theory, and the experimental techniques Varela designed to examine this quality have been applied to research fields such as computer sciences and artificial intelligences. Therefore, the immune network theory is not only creating a paradigm shift in immunology, but also bringing about revolutionary changes in other disciplines.

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Acknowledgement

This thesis is the result of a serendipitous encounter with Francisco Varela's work in immunology. In addition to bringing together my background in both science and history, readings on Varela's understanding of epistemology and Buddhism have truly been a spiritual journey for me. I would like to thank my parents for being with me every step of the way. Even though they are no longer with me physically, I have them always in my heart. *Thanks, Mom, Dad!* I would also like to thank my dog Spike, who put up with endless hours of my sitting in front of the computer instead of taking walks with him. My friends and colleagues, who were always there to encourage and support me in the most stressful and lonely moments, are deeply appreciated. The faculty and staff of the History Department, especially the late Jennifer Kho who had assisted me with all the conferences I organized for professors, are also appreciated. In addition, there are two people to whom I would like to express my gratitude individually: Prof. Carla Nappi, whose intellectual generosity and tireless editing of drafts after drafts of my thesis have made me a much more responsible and careful writer; and, Prof. Keith Benson, who has always been there to offer new perspectives and helpful hints when my ideas where exhausted. Finally, an incredibly big thank you to my supervisor, Prof. Robert Brain, without whose advice, guidance, and support, I would never have the courage to undertake this project. Your brilliance and creativity have been the source of this project since the very beginning. Thank you.

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For my mom,

Love never ends . . .

Introduction

The country of Brazil was an unlikely birthplace of any forms of revolutionary thinking in the 1980s. Since the coup d'état of 1964, which culminated to the overthrowing of President Joao Goulart, Brazil and its people had been subjected to a series of military dictatorships that would not come to an end until nearly three decades later. The effects of the oppression were far-reaching. During this period, many scholars and scientists were coerced into resigning from their positions, while some simply went into exile.[1] Despite this, a few public institutions struggled to maintain their intellectual autonomy, and one of which was the Sociedade Brasileira para o Progresso da Ciencia (SBPC). "The SPBC remained," as immunologist Antonio Coutinho reminisced in his personal note, "very much a stronghold of opponents to the autocratic regime and a rare forum for free exchange of ideas in the country."[2] As the Sociedade brought together a group of renowned scientists from around the world in 1982 under these unique circumstances, it was befitting that what was discussed at the meeting would lead to impacts of great importance.

Convened by immunologist Nelson Vaz, the principal aim of the Conference was to consider the current state of theoretical immunology and its future.[3] At the time, and still to this day, there were two opposing views on the emergence of immunity and how it ought to function in relation to the body. On the one hand, there was the Clonal Selection Theory (CST) by Frank MacFarlane Burnet, which fostered the imagination of the immune system as a defense and attack system. This theory had guided the development of immunological thinking since its articulation in 1957. On the other hand, there was the new organism-centered immune network theory proposed by Francisco Varela in 1978. The significance of this issue of two contending

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[1] O. A. Sant'Anna, "Immunology in Brazil: historical fragments," *Scandinavian Journal of Immunology* 66 (2007): 110.

[2] Antonio Coutinho, "A walk with Francisco Varela from first- to second-generation networks: In search of the structure, dynamics and metadynamics of an organism-centered immune system," *Biological Research* 36 (2003): 18.

[3] Francisco Varela collaborated with Nelson Vaz on "Self and Non-Sense: an organism-centered approach to immunology," in which the two outlined the theoretical principles and research program of an immune network.

theories of immunity matters beyond determining how our bodies overcome pathological challenges, for it is concerned ultimately with the perpetuation of life and its evolutionary competitiveness against the pressure of natural selection. It was at the SBPC meeting where opinions of these two camps collided, and also where dialogues leading to foundational changes began to take shape.

As scientists were still accustomed to considering immunity along the lines of Burnet's framework, Varela's theory met with varying degrees of skepticism when it was first proposed in the late 1970s. In the 2000s, a sufficient amount of experimental findings had led scientists to begin to acknowledge its strength. Since, their views have changed, while many, including Varela's former colleagues and collaborators such as Antonio Coutinho and John Stewart, have gone as far as to claim the discipline of immunology is undergoing a paradigm shift.[4] However, scholarly efforts to study the importance of this transition have been sorely lacking. The most comprehensive work in the English language to date is Arthur Silverstein's *A History of Immunology*, which chronicled the development of immunology up to the first half of the twentieth century. There has also been Alfred Tauber's *the Immune Self*, in which he discussed the use of the self as a predominant metaphor in the theoretical development of both Burnet and Varela's theories, respectively, and compared briefly their differences. However, this was still, by and large, a disjointed narrative.

My work attempts to add to the existing scholarship by arguing that this ongoing theoretical shift in immunology has in part been historically and culturally motivated. This is to say that the metaphoric language Varela used to describe the purpose of immunity and the

[4] In addition to Varela and Vaz's "Self and Non-Sense," there have been several publications devoted to discussing the issue of an ongoing paradigm shift in immunology since Varela's premature death in 2001. Alfred I. Tauber, *The immune self: Theory or metaphor?* (Cambridge: Cambridge University Press, 1994); Irun R. Cohen, *Tending Adam's Garden: Evolving the Cognitive Immune Self* (New York: Academic Press, 2000); Uri Hershberg and Sol Efroni, "The Immune System and Other Cognitive Systems," *Complexity* 6 (2001): 14-21; and, John Stewart, "The Affirmation of Self: A New Perspective on the Immune System," *Artificial Life* 10 (2004): 261-276.

behaviour of the immune system, and to shape accordingly a research program, was very much molded by his political philosophical reflection of the events that occurred in Chile in the late 1960s and the early 1970s. Further, its history as the Latin American country with the longest period of uninterrupted democratic rule from 1932 to 1973 and as a member of the non-Aligned movement since the 1960s also contributed to the forming of his worldview. Throughout his life, Varela emphasized repeatedly the notion of self-determination and its two characteristics, autonomy and individuality. Even though Varela's focus was on Chile, the pursuit of these ideals was a burgeoning phenomenon worldwide. In other words, what was transpiring at the SBPC meeting, namely, the revising of Burnet's theory in favour of Varela's, coincided closely with changes in world politics in the 1970s.

This thesis examines how Varela came to conceive his immune theory, focusing largely on the use of the network metaphor to espouse a notion of selfhood arising from global cooperation and connectivity. The first section presents an account of the beginning of immunity being perceived as a defense mechanism by Russian scientist Elie Metchnikoff at the end of the nineteenth century. In many sense, this imagination set the stage for Frank Burnet's theory. The second section examines the relation between Varela's theory and metaphors, and how they differed from that of Burnet's in the most fundamental way. The third section deals with how, when a research program was tailored to meet Varela's vision, it transformed the landscape of immunology at the most basic point where laboratory equipment was designed and specimen organisms were prepared. I delve into Varela's philosophy in the fourth section, studying how the network portrayal of immunity in large part originated from his experiences of the political chaos in Chile. The events leading up to the violent seizure of power by General Augusto Pinochet in 1973, during which the lives of tens of thousands of people, some of whom were Varela's closest friends and colleagues, were lost through murder and torture. In the final section,

I conclude by remarking on how impacts of Varela's immune theory have also extended as broadly as to research areas such as artificial intelligence and computer security system.

A History

Embryologist Elie Metchnikoff was the first to lay the foundation of the modern day understanding of immunity at the end of the nineteenth century. Born in the Steppe region of Russia in 1845, he was the youngest son of Ilya Metchnikoff, a retired Guard officer, and Emilia Metchnikoff. After graduating from the University of Khar'kov in 1864, Metchnikoff went to Europe and worked in different laboratories in Germany, Switzerland and Italy for a number of years. Working predominantly with marine species, Metchnikoff was famously known for his work on the digestive tracts of organisms such as starfish and sea anemones.[5] During this period, he made prolific contributions to the study of the anatomical developments of invertebrates and their comparative connections in evolution.

In 1883, Metchnikoff presented the theory of phagocytosis, for which he would be awarded the Nobel Prize in Physiology and Medicine, together with the German immunologist Paul Ehrlich, in 1908. It was perhaps the most important work in his career. In this theory, Metchnikoff used findings he gleaned from observing the functions of the digestive and blood cells of various invertebrate species to hypothesize the role of the phagocytes. According to Metchnikoff's chief biographers Alfred Tauber and Leon Chernyak in *Metchnikoff and the Origins of Immunology*, he believed that the extending of threadlike tentacles (namely, pseudopods) by these amoeboid cells to surround and destroy foreign bodies was in actuality a defense mechanism. "These are the cells [phagocytes] which betake themselves to situations where micro-organisms and their poisons make their appearance," he stated, "and which manifest a reaction against them."[6] In addition to adopting the word "engulfing" to describe the action of the phagocytes, Metchnikoff also put forth two important concepts. First, he termed their capacity to actively protect the organism from infection as immunity; and, second, he

[5] Paul De Krulf, *Microbe Hunters* (New York: Harcourt, Brace and Company, 1926), 201-227.
[6] Elie Metchnikoff, *Immunity in Infective Diseases*, tran. Francis G. Binnie, in the Biodiversity Heritage Library, www.biodiversityheritagelibrary.org/item/75391 (accessed Janurary 14, 2012).

argued that their aim was to harmonize the intrinsically disharmonious internal environment of the organism, which was a result of constant exposure to bacteria.[7]

In 2008, this combative portrayal was further expounded upon by Kirill Rossiianov in "Taming the Primitive." Unlike Tauber and Chernyak who focused on Metchnikoff's philosophical exposition of the interconnections between phagocytes and organisms, Rossiianov was interested in how his understanding was influenced by the racist anthropology that emerged in nineteenth century Russia.[8] As he undertook this task, Rossiianov pointed out that Metchnikoff had compared the phagocytes to the armies conscripted by European powers in their African colonies in one of his earliest publications. As Rossiianov quoted, Metchnikoff had stated, "the organism that fights against the lower plants [i.e., bacteria] deploys such elements that most of all remind the lower animals - against the bacteria it sends the army of amoeboid cells."[9] Since the early days of its conception, immunity has been couched in a martial rhetoric where the physical boundary of an organism is highly guarded through the mobilization of special cells.

This idea became a critical framework in which subsequent immunological theories flourished. When antibodies and their ability to prevent and cure infectious diseases were discovered also in the 1880s, it seemed logical to perceive them as the *de facto* representation of immunity. Indeed, studies of these proteinaceous compounds continued in this vein well into the twentieth century. However, as the contemporary methodological approach in the biological sciences was very much suffused with the reductionist ideal, research emphases were devoted primarily to investigating the biochemical properties of antibodies as constituents of immunity. Decades of studies culminated to the formation of a landmark theory that came to underpin the

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[7] Leon Chernyak and Alred I. Tauber, "The Idea of Immunity: Metchnikoff's Metaphysics and Science," *Journal of the History of Biology* 23 (1990): 187-249.
[8] Kirill Rossiianov, "Taming the Primitive: Elie Metchnikoff and His Discovery of Immune Cells," *Osiris* 23 (2008): 213-229.
[9] Rossiianov, 214.

corpus of modern immunological knowledge. It was the Clonal Selection Theory of Acquired Immunity (or, the CST); and, it was in this theory that immunity received most of its scientific endorsement as a form of biological defense.

Proposed by virologist Frank MacFarlane Burnet in 1957, the CST sought to explain many of the observed immune activities for the first time, including the physiological circumstances that prompt the production of antibodies to bring about immunity. In *The Clonal Selection Theory of Acquired Immunity*, Burnet explained that, in the case of vertebrates, a recognition mechanism arose at the end of embryonic stage to differentiate "self components from 'non-self'" such that "all possible types of foreign and antigenic determinants can be positively recognized as foreign and hence calling for an immune response."[10] In "Genetics and Immunology," he went further to describe vividly that this would amount to "destruction by appropriate enzyme systems."[11] In other words, according to Burnet, immunity was to protect the body (self) by neutralizing foreign matters (non-self) with specific antibodies.

In the respect of providing defensive means, Frank Burnet and Elie Metchnikoff shared a similar understanding. However, unlike Metchnikoff, whose principal concern was the maintaining of the organism's internal harmony, Burnet spoke almost exclusively of its ability to engage in warlike responses against the external enemy. By doing so, he found a generation of receptive audience in the 1950s. The time was after the Second World War; the Allies had successfully stymied the expansionist agenda of both Japan and Nazi Germany, and the United States and the Soviet Union had just emerged as the two opposing new hegemonic powers. In the midst of an international chaos, the sense of security provided by Burnet's triumphalist view was not only a great comfort to those were distressed by the uncertainty of the era, it was also a beacon of hope in facing any potential attacks. Just as capitalism was destined to defeat

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[10] Frank MacFarlane Burnet, *The Clonal Selection of Acquired Immunity* (Nashville: Vanderbilt University Press, 1959), 46.
[11] F. M. Burnet and F. Fenner, "Genetics and Immunology," *Heredity* 2 (1948): 315.

communism, the human race would prevail over these ruthless pathogens. Ideologically as well as scientifically, this self and non-self discrimination model provided an unquestionable convenience in explaining the purposes of immunity, and, as a result of this, it became deeply entrenched in the immunological thinking.

However, progress in cellular immunology and immunogenetics since the 1960s generated a considerable amount of contradicting evidence that brought Burnet's theory into question. The most notable issue that scientists took was with its adequacy in making sense of the occurrences of autoimmunity and lymphocyte diversity. In 1978, neurophysiologist Francisco Varela suggested an alternative approach to interpret immunity and its behaviour. In a seminal paper titled "Self and Non-Sense," he articulated the model of "self-determination." Contrary to most scientific publications that placed a strong emphasis on exhibiting experimental data, Varela sought instead to provide "a conceptual framework to accommodate important recent developments in immunology."[12] "This paradigm," Varela stated in the abstract, "represents almost a logical inversion of the Burnetian idea of self-discrimination." As Varela continued further to highlight its characteristics, he described immunity as a biological phenomenon fostered by the connectivity and cooperativity of the cellular components of the organism, and was thus capable of determining the relevancy of foreign elements to itself. To encapsulate these concepts, he looked to the metaphor of network.

It was a stark contrast to the battlefield-like construct conceived by Metchnikoff and, in many ways, inherited by Burnet. Even though this was the case, metaphors of immunity had historically owed much of their credibility to the broader political and social conditions in which they were conceived. The story of the immune network was no exception. In the subsequent

[12] N. M. Vaz and F. J. Varela, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 231.

sections, I explore some of the key factors surrounding Varela and their influences on the formation of his theory.

The Theories and the Metaphors

Scientists have routinely relied on the explanatory power of metaphors to bridge the limitation of human imagination in understanding the complexity of life. As such, modern biology is replete with metaphors: white blood cells as soldiers, genes as codes, and self-regulatory processes as feedback loops. While the historiography on the subject of scientific metaphors is both vast and rich, two books in particular laid the foundation. In *Crystals, Fabrics and Fields*, Donna Haraway pointed out the value of this linguistic practice. "An important aspect of a paradigm is metaphor," she stated succinctly, "and it is suggestive to investigate the use of metaphor to direct research and its interpretation."[13] Keeping in line with this contention, Haraway undertook an extensive study on the impact of the metaphor of organism on embryology and how, as it influenced the ways by which embryologists such as Ross Harrison, Joseph Needham, and Paul Weiss interrogated the formation of the embryo, the discipline was transformed in the beginning of the twentieth century.

The second book is *Refiguring Life* by Evelyn Fox Keller. In it, she attributed the power of metaphor to the performative nature of language. Drawing from the theory of "speech-acts" laid out by J. K. Austin in a series of lectures at Harvard University entitled *How to Do Things with Words*, Keller took a step further to make an important argument. ". . . descriptive statements are performative in a rather different sense from that of speech-acts: not by virtue of directly enacting their referents," she contended, "but by their purchase on the ways in which we structure and construct our social and material worlds."[14] That the fact that certain words possessed a greater efficacy than others in helping to shape the world we live in was because

[13] Donna Jean Haraway, *Crystals, Fabrics and Fields: Metaphors of Organicism in Twentieth-Century Developmental Biology* (New Haven: Yale University Press, 1976), 2.
[14] Evelyn Fox Keller, *Refiguring Life: Metaphors of Twentieth-Century Biology* (New York: Columbia University Press, 1994), xi.

they resonated more with the social conventions and cultural norms of the time.[15] To illustrate this point, Keller used geneticists' discourse of gene action, Erwin Schroedinger's attempt to reconcile the second law of thermodynamics with the stability of genetic memory, and the transformative force that the age of computer had on our conceptualization of the body as examples. In this section, I extend both Haraway and Keller's analyses, respectively, into immunology to shed new light on the theoretical development of the discipline.

In comparison to other sciences, the institutionalization of immunology came fairly recently even though entities such as macrophages, antigens and antibodies had been identified since the late nineteenth century.[16] In *Toward an Anthropology of Immunology*, Emily Martin stated, "It was generally not until the 1970s that departments of immunology existed in American and other universities."[17] However, despite being a latecomer, it has relished an eventful existence. In the entirety of the history of the discipline, two distinct models of the immune system have been proposed: one by Frank Burnet and the other by Francisco Varela. While they both adopted the self as a pivotal concept, how its reciprocal relationship with immunity was defined and construed differed drastically in each theory. And, the point where their differences can be most clearly distinguished was in the metaphors they used.

In the introduction of "Self and Non-Sense," Varela summed up the core of his theory in approximately fifty words. "[The] immune system as a closed network of interactions which self-determines its ongoing pattern of stability and its capacities of interaction with its environment," he stated, "Thus, all immune events are understood as a form of self-recognition, and whatever falls outside this domain, shaped by genetics and ontogeny, is simply non-sensical."[18] The main

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[15] Keller, xii.
[16] Emily Marin, "Toward an Anthropology of Immunology: The Body as Nation State," *Medical Anthropology Quarterly* 4 (1990): 416.
[17] Martin, 416.
[18] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 231.

task of the immune system, therefore, was to "declare whether the contact with the molecule was immunologically relevant or not."[19] In other words, what was deemed irrelevant to the self would simply not enter the realm of consideration for the immune system, according to Varela. This was fundamentally difference from Frank Burnet's theory, which contended that entities that were perceived as foreign were unquestionably destroyed, irrespective of their affinity to the self. To highlight this distinction, Varela purposefully titled the paper "Self and Non-Sense," a wordplay on Burnet's self versus non-self discrimination idea.

Not only was the concept of relevance crucial, it also became the foundation of Varela's theory. In "Self and Non-Sense," he devoted a great amount of efforts to explain its importance in understanding immune responses. According to Varela, organic entities were understood in terms of their relevance, which was not dependent upon their inherent properties but upon their relation to the organism's genetic background and immunological history. Whereas irrelevant materials are deemed inconsequential, relevant substances would interact with one another cohesively to constitute "the immunological self of the organism." From here, Varela took another theoretical leap to argue that the immune activities of an organism would only be " . . . self-referential, performed in reference to the self."[20] This meant that immunity functioned to determine its own domain of interactions with the external environment, according to Varela. He pointed out the significance of this extrapolation to his work, "To develop this new conceptual framework [a immune network], we must understand initially that we may only talk about immune events in a relational or referential way."[21] From relevance to reference, Varela found the theoretical beginning of the self for his immune theory.

[19] Varela and Vaz, 246.
[20] Varela and Vaz, 238.
[21] Varela and Vaz, 232

As Varela continued, he reflected on how revolutionary this idea was, " . . . a notion which has not been applied to immunology, although it has been successfully applied to the description of other complex systems."[22] To explain, he stated, "Such interactions [self-referencing] we refer to as connectivity gives rise to a lymphoid network comprising the totality of the lymphoid tissues."[23] This statement is crucial in two meaningful ways. On the one hand, it stated an image of the immune system with which Varela saw only fit to use the metaphor of network to describe. That is, it was a "complex interconnected system" that foregrounded the cooperativity of all of its constitutive components.[24] On the other hand, and as a result of the first characteristic, he hinted that such a system needed to be considered as an irreducible whole, incapable of being examined from the perspective of a singular cell type. When Varela proposed his theory in 1978, he could not have elaborated further on these points because of the technological limitations of the time. However, in a 1991 paper titled "Second Generation Immune Networks," he certainly did so with his co-author, immunologist Antonio Coutinho.[25] Together, self-determination and self-reference became the two key principles of Varela's conceptual framework.

While Varela looked to the metaphor of network for inspiration, it in return strengthened his theory. With its powerful image, he put forward an even more vital implication to suggest a shift in the perspective of how the self of an organism was immunologically established. In

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[22] Varela and Vaz, 232.

[23] Varela and Vaz, 237.

[24] Varela and Vaz, 238.

[25] Francisco J. Varela and Antonio Coutinho, "Second generation immune networks," *Immunology Today* 12 (1991): 159-166. As the title of this paper suggested, Varela and Vaz were not the original creators of the idea of the immune system as a network. Instead, Danish immunologist Niels Jerne was credited as the pioneer. In a 1974 publication titled "Toward a Network Theory of the Immune System," Jerne proposed the idiotypic network theory. According to Silverstein's research in *A History of Immunology*, Jerne's idea lead to a considerable amount of research interests in the ensuing years. However, the particular immuno-regulatory processes suggested by Jerne were simply too controversial to obtain any conclusive empirical data. Despite this, Jerne's contributions were mentioned in "Self and Non-Sense," in which Varela and Vaz wrote, "This paradigm [organism-centered, immune network], stemming from the idea of Jerne . . . " In many sense, Varela and Vaz rescued this metaphoric depiction of the immune system in the late 1970s.

Burnet's framework, it was externally imposed, which meant, without the juxtaposing of non-self materials to initiate the discrimination mechanism, self would not have been otherwise distinguished. Varela, on the other hand, held an entirely different view. According to him, self was internally defined and to which every immune response referred.[26] Therefore, for this hypothesis to hold true, Varela contended, there must have been a pre-formed self that had already been in existence before the organism had any contact with foreign materials. The most foundational distinctions between the two immune theories, in his own words, involved "a change in our referential standards: from an antigen-centered immunology to an organism-centered immunology."[27] In other words, Varela dismantled the bi-polar division between "us" and "them" that permeated Burnet's language in the 1950s.

As Varela took issue with Burnet's theory of self versus non-self discrimination, he also argued against its representation as warfare. It was here that the development of his idea of the immune system was most evidently seen as a reflection of the broader political and social conditions of the 1970s. This point was especially poignant when Varela, who was in Chile at the time, was witnessing crises being fomented by two competing ideological powers from the periphery.[28] The idea of an immune network as an irreducible whole no longer depicted this biological system reductionistically as a defense system that retaliated against any attacks by foreign enemies (antigens) with equal force (antibodies). Varela stated in "Second Generation Immune Networks":

> . . . simple agents are dynamically connected to each other in dense ways. Each such component agent operates strictly on the basis of its local environment but, because of the system's network constitution, there is a global co-operation which spontaneously emerges as the states of all participating components become mutually satisfactory. In such a system, there is no need for a central processing unit to guide the entire operation, and the external impacts do not turn the system's axle. External stimuli modify only the

[26] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978):
[27] Varela and Vaz, 236.
[28] Odd Arne Westad, *The Global Cold War* (Cambridge: Cambridge University Press, 2007)

> local environment of individual components (which will behave according to conventional stimulus-response patterns), but the system's operation and properties will always emerge from global co-operativity. This passage from local rules to a new emergent property of the entire system, which cannot be reduced to the quality of performance of single components, is the very heart of network mechanism.[29]

According to him, the notion of a militarized body was to be replaced by three key characteristics instead. First and foremost, there was an emphasis on global cooperation fostered by the interconnectedness of the components. Its purpose was to create a harmonious state of existence within the body. The second was the decentralization of the immune system in the service of encouraging regionalized responses to the outside environment. Last, the autonomy and individuality of such a system, including its constituents, were always preserved, irrespective of external changes.

The necessity for this theoretical shift in understanding the immune system, thereby its metaphoric representation, was also affirmed experimentally. There were mainly four reasons. First, according to Burnet's martial construct, the emergence of immunity relied on antibodies to recognize the specific antigen that evoked it. Using the mammalian immune system as an example, this type of antigen-antibody specificity was estimated impressively to be the order of 10^{17}. Further, the underlying assumption of Burnet's framework was that the repertoire of antibodies was complete, meaning that the immune system was capable of identifying foreign material of all possible molecular shapes, including those it had never before encountered.[30] However, experiments had produced findings that contradicted this hypothesis, as the specificity of immune system had been discovered to be limited, or in Varela's own words, "rather degenerated." This meant "there are no one-to-one relationships in immune events."[31]

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[29] Francisco J. Varela and Antonio Coutinho, "Second generation immune networks," *Immunology Today* 12 (1991): 159.

[30] John Stewart and Antonio Coutinho, "The Affirmation of Self: A New Perspective on the Immune System," *Artificial Life* 10 (2004): 261-276.

[31] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 239. See also S. S. Spring and A. Nisonoff, "Idiotypic specificity as a probe for investigating

Second, contrary to Burnet's self versus non-self discrimination notion, studies indicated that antibodies could in actuality bind randomly even to each other under normal circumstances, thus leading to self-destruction. In immunology, this occurrence is known as autoimmunity. Yet, this phenomenon is uncommon is suggestive of the immune system's innate ability to recognize it own components.[32] The third was the issue of lymphocyte diversity. As opposed to Burnet's postulation that each cell clones was able to produce only one, or very few types of antibodies in the prenatal period, it had been discovered that there were an immense variety of antibodies in adult vertebrate organisms.[33] Last, in contrast to Burnet's assumption that the immune system could develop only as a result of being stimulated by presence of foreign materials, a significant amount of evidence have indicated that even when confined in complete isolation, a full-blown immunity could still arise in an almost instinctual manner.[34] In Varela's opinions, a self-determining, self-referencing immune network that emphasized the cooperativity and interconnection of its parts could rectify these discrepancies.

In many ways, these were the qualities that echoed well with the backbone of Varela's political philosophy. Even though his immune theory was considered radical by many immunologists, the optimism they conveyed was well received. As I continue my narrative, this point will become increasingly clear, culminating in the final section where I discuss Varela's reflection on the political and civil turbulence in Chile in the 1970s and how they came to influence and shape his worldview. Ultimately, this transition from one immune theory to

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persistence and changes in clones of cells producing immunoglubulins," *Contemporary Topics of Molecular Immunology* 2 (1973): 99.

[32] G. Torrigiani, D. Doniach, and I. M. Roitt, "Serum thyroglobulin levels in healthy subjects and in patients with thyroid diseases," *Journal of Clinical Endocronology* 29 (1969): 305.

[33] D. J. Katz and B. Benacerraf, eds. *Immunological Tolerance: Mechanisms and potential clinical applications* (New York: Academic Press, 1974).

[34] Fritjof Capra, *The Web of Life: a new scientific understanding of living system* (New York: Anchor Books, 1996): 269.

another can be viewed as a microcosm of the changes of the wider global politics in the post-1954.

The Experiments

While the metaphor of network played an important role in Varela's conceptualization and the development of his immune theory, an even larger part of its success rested in its performative capacity. As Donna Haraway and Evelyn Fox Keller had asserted, metaphors became the language with which scientists used to direct research programs. In Varela's case, it translated into two emphases - the totality of the immune system and the interconnectedness of its constitutive parts. Together, they aimed to maintain as attentively as possible the wholeness of the organism specimen during experimentation. When Varela tellingly incorporated the notion of "organism-centeredness" in to the title of his theory, he had perhaps already hinted at this orientation. In this section, I focus on the characteristics of such a research program and its differences from Burnet's reductionist treatment that took into account solely the capability of the immune system to defend and attack. Further, Varela's focus on the importance of preserving the whole of the organism was also related directly to a broader shift in methods of examining biological phenomena in the second half of the twentieth century, that is, from reductionism to wholism.[35]

Keith Benson was the first to remark on this underlying attribute in Varela's thinking in "Biology's Phoenix," " . . . the properties of the component parts of a living system do not determine its properties as a unity," he explained, "the properties of a self-maintaining system are determined by the unitary organization."[36] In other words, to examine such a system, its unity must be maintained. Further, as a contrast, Benson also remarked on how principles of reductionism had been used in biological investigations. He stated, " . . . [It] involved the reduction of biological explanations to principles borrowed from physics and chemistry: to study the organism, it was teased into its constituent parts, the phenomena associated with these parts

[35] Keith R. Benson, "Biology's "Phoenix": Historical Perspectives on the Importance of the Organism," *American Zoologist* 29 (1989): 1067-1074.
[36] Benson, 1072.

were explained at the lowest level of organization and, consequently, the emphasis on the whole of the organism gradually became lost."[37] Experiments designed in accordance to Burnet's Clonal Selection Theory bore many of these qualities. In his conclusion, Benson contended that Varela's theoretical work was an example of the revival of the organism in the biological sciences after a long and contentious relationship between these two methodological traditions that had begun since the late nineteenth century.[38]

Burnet's theory was reductionistic in nature because, in the defense and attack setup, the development of immunity was stripped down to a series of selection decisions. According to the Clonal Selection Theory, materials identified as foreign were destroyed swiftly; and, the identification of their presence was made possible by removing all protein receptor that recognize the self-components in the prenatal stage of the immune system. To study this process, scientists had conventionally directed their attention to the cellular and molecular activities of the lymphoid tissues involved. This typically meant the two primary lymphoid sites, the epithelial cells of the thymus and the bone marrow. Procedurally, the first step had been to standardize the genetic makeup of the organism specimens. This was done through successive inbreeding of mice - generally after ten to twelve generations - to obtain congenic resistant strains.[39] The objective was to minimize as much as possible contamination from other unwanted genetic elements while attempting to isolate the allele of a selected antigen receptor. The resultant mice

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[37] Benson, 1067.

[38] It needs to be noted that Varela's immune theory was an application of the theory of autopoiesis, which he had created with Humberto Maturana. In addition to immunology, autopoietic theory has also been used in the context of neurobiology and endocrinology. It was published originally in Chile in 1972 under the title *Autopoiesis: The Organization of the Living*, and republished again in 1980 under the title *Autopoiesis and Cognition: the Realization of the Living* (Holland: D. Reidel Publishing Company, 1980). This subject is discussed formally in the fourth section of this paper. In "Biology's "Phoenix,"" Benson's focus was strictly on the general characteristics of autopoietic theory, without delving into a specific discipline. However, the key principals of a self-determining, self-referencing system that foregrounds the unitary organization of its components parts remained the same.

[39] William R. Clark, *The Experimental Foundations of Modern Immunology* (New York: John Wiley & Sons, Inc., 1991): 466. In genetics, organisms that differ in one locus on their respective gene allele are defined as congenic. Typically, in immunological research, it is the locus linking to histocompatibility genes, which were then translated into proteins involved in the selection process.

that were homozygous in this allele were then irradiated to remove traces of any developed immunity.[40] This step ensured the immune system of the mice was at its most innate state. Finally, transgenic genes carrying identifiers were introduced into the mice, and, as their immune system reconstituted and matured, selection between self and non-self components began.[41] To project outcomes, differential equations were generally formulated. This type of mathematical modeling was the predominant technique in these experiments. In *the Clonal Selection Theory of Acquired Immunity*, Burnet stated, "My own working picture of the situation is frankly based on a desire to obtain the simplest interpretation of the cellular basis of antibody productions."[42] Even though these equations might have been elaborate and complex, he also acknowledged the straightforwardness of this approach and its reductionist nature.

The excessive genetic tempering of organism specimens, the narrow focus on only certain types of lymphoid tissues, and the use of artificial situations to mobilize the immune system met Varela's questionable eye. In his view, the complexity of the immune system could not be demonstrated fully in this manner, especially via differential equations that were intended to embody laws of physical sciences. This seemed to be the consensus amongst other immunologists as well. In a 2000 paper titled "The Emergence of Spatial Complexity in the Immune System," Yoram Louzoun *et. al.* stated, "differential equations have revealed their power in physics and chemistry, and so biology has seen fit to use the language of the differential

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[40] Clark, 320. The amount of radiation subjected to the organism specimens were typically set at a sublethal dosage of 1000R.

[41] Frank MacFarlane Burnet, *The Clonal Selection Theory of Acquired Immunity* (Cambridge: Cambridge University Press, 1959). Burnet gave a written account of how experiments were carried out in Chapter Three and Four, "The Facts of Immunity and "The Clonal Selection Theory of Antibody Production," respectively. See Chapter Thirteen, "Immunological Tolerance, " in William R. Clark, *The Experimental Foundations of Modern Immunology* for a clearer diagrammatic depiction. As the complexity of the procedures of the actual experiments was well beyond the scope of this paper, I sought only to present a general overview of what a typical experiment shaped by Burnet's theory entailed. Furthermore, the identifiers were usually antigens of various types with which immunologists used to observe their effects on the immune system.

[42] Frank MacFarlane Burnet, *The Clonal Selection Theory of Acquired Immunity* (Cambridge: Cambridge University Press, 1959).

equation to try and understand the complexity of living systems."[43] A great detriment of this approach, they continued, was that:

> . . . individual differences between discrete elements in a system are neutralized by their being lumped into average characteristics of interest. The power of differential equations is in their assumption that the local "average" embodies more truth than does the collective of individual microscopic differences, which are always susceptible to chance sampling errors.[44]

In retrospect, this somewhat cautionary view highlighted precisely not only the essence of an "organism-centered, immune network," but also what needed to be achieved in the modeling of this theory. That is, the goal to affirm self while preserving its idiosyncrasies.

In "A Walk with Francisco Varela from first- to second-generation networks," a commemorative article written two years after Varela's premature death in 2001, Antonio Coutinho recounted how it could be made possible by giving more "attention to the biology of the cells that produce such antibodies."[45] In many respects, this statement pointed to a question that dealt most pertinently with the preparation of the organism specimen. At the concurrent time, it also offered a solution. The rational behind Coutinho's argument was simple. At any given moment, the immune system was not constituted by the antigen receptors that genetic inbreeding attempted to single out, but by a multitude of cells such as the suppressors, memory cells, and helper T- and B-cells. Varela made a similar remark in "Self and Non-Sense," " . . . all lymphocytes of the organisms are involved in all immune events;" therefore, it became crucial to use "normal lymphoid cell population - or better yet, normal organism" during experimentation to create conditions that resembled as closely as possible the actual biological state.[46] Continuing

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[43] Yoram Louzoun, *et. al.*, "The Emergence of Spatial Complexity in the Immune System," *Condensed Matter* 33 (2000): 2, in Cornell University Library, www.arxiv.org/html/cond-mat/0008133v1 (accessed on January 1, 2011).
[44] Yoram Louzoun, *et. al.*, 2.
[45] Antonio Coutinho, "A Walk with Francisco Varela from first- to second-generation networks: In search of the structure, dynamics and metadynamics of an organism-centered immune system," *Biological Research* 36 (2003): 18.
[46] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 247.

in this vein of using normal organism specimen, Varela also urged the abolishment of the irradiation method. Though it was intended as a means to provide standardization, the effects were disruptive to the internal stability of the immune system, which was otherwise highly regulated.[47] In other words, Varela argued that to maintain the characteristics of the immune system that were self-determination and network-like interconnectivity, it was necessary to first restore the somatic totality of the organism specimen.

With respect to designing an experimental model, there was a proposed shift towards using computational means instead.[48] This was necessary because mathematical modeling, namely, the use of differential equations, was inapplicable to "the assessment of these more global activities of the lymphoid network."[49] Indeed, for the restoration of the organism specimen to become completely meaningful, it also needed to occur at the level where its properties could be ascertained. This new approach developed broadly in two phases. First, the formative stage was around the time of the publication of "Self and Non-Sense." In it, Varela contended that one of the central features of an immune network was a controlled balanced between excitatory and inhibitory mechanisms.[50] Its purpose was to ensure that "the whole of interactions undergoing in the lymphoid system eventually closes onto itself."[51] This recursive behaviour, Varela continued to explain, "[is] a highly complex phenomenon, embodying the dynamics of the mutual interdependencies of the components of the lymphoid system in sequential moments of time. The system's actions are such that they affect the system's

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[47] Varela and Vaz, 247.

[48] Although Varela had already had a clear idea about using techniques other than differential equations to build his model of an immune network in "Self and Non-Sense," the term "computational" was first used by Alfred Tauber to describe this new method. See Alfred I. Tauber, *The Immune Self: Theory or metaphor?* (Cambridge: Cambridge University Press, 1994): 195-197. In addition, it was also referred to as microscopic simulation (MS) methdology by Yoram Louzoun, *et. al.*. See Yoram Louzoun, *et. al.*, "The Emergence of Spatial Complexity in the Immune System," *Condensed Matter* 33 (2000):2.

[49] Yoram Louzoun, *et. al.*, 2.

[50] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 247.

[51] Varela and Vaz, 247.

recognition. Conversely, the system's recognition . . . accounts for its subsequent actions . . ."[52] In other words, as a result of a series of self-regulatory activities, a circular causality with constant changing states of stability was created; and, Varela regarded this quality as equivalent to self-determination.[53]

While recursion was an exceedingly common biological phenomenon, the complexity of its non-linearity was beyond the scope that is fathomable by differential equations. In the case of the immune system, this was so because the embedded reductionist assumption treated it as a linear input-and-output, or defense and attack, construct.[54] Even though there had been efforts attempting to use pure mathematical means to examine the immune system as a whole, Varela felt the demand of "detailed knowledge of the cellular interactions occurring in the system" inevitably distracted attention from the coordination of its constitutive components.[55]

The second phase came in the 1990s. If the need for computational modeling were not as pronounced in the 1970s, this realization had certainly deepened by then. During this period, Varela looked specifically at the interconnectivity between lymphocytes, and attributed the slow development of the network theory to the neglected treatment of this characteristic by most immunologists.[56] The previous attempts that did take it into consideration, as he contended, were still subjected to the overarching influence of Burnet's theory.[57] "Some elementary network ideas have been uncritically 'grafted' onto mechanism that are proper to Clonal Selection Theory," Varela stated, "but the two theoretical frameworks occupy distinct domains and address

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[52] Varela and Vaz, 247.
[53] Varela and Vaz, 247.
[54] John Stewart and Antonio Coutinho, "The Affirmation of Self: A New Perspective on the Immune System," *Artificial Life* 10 (2004): 261-276.
[55] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 231-267.
[56] Francisco J. Varela and Antonio Coutinho, "Second generation immune networks," *Immunology Today* 12 (1991): 159.
[57] Varela and Coutinho, 159.

different levels of description of the immune system."[58] In other words, the vision of a true network, as Varela had intended, had yet to be realized.

The emphasis on interconnectivity came with the introduction of two important concepts. They were dynamics and metadynamics; they shared two similarities. First, in interacting with one another, a circular, recursive relationship was formed between them. Second, they both concerned with the configuration of a very specific region on lymphocyte receptor protein known as the Variable region, or simply as the V region. The dynamics monitored the concentration of this region in the immune system since any increase would bring about the activation and production of antibodies. The purpose was to distinguish active lymphocytes from those that were in a resting state, which, according to Antonio Coutinho, "contribute little or nothing to the network structure, which was built by serum antibodies and the cells that produce them."[59] In other words, the development of immunity hinged on a very tightly regulated balance.[60]

On the other hand, the metadynamics was what Varela believed to give a genuine immune network its uniqueness.[61] "Since the V regions are unique," he explained the theoretical root of this concept, "the dynamics of the system constantly changes, producing novel configuration." According to Varela, metadynamics addressed the supraclonal properties that emerged from the network organization of the immune system.[62] It concerned with the recruitment of lymphocyte clones directed at the V regions, which in turn would lead to the

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[58] Varela and Coutinho, 160.

[59] Antonio Coutinho, "A walk with Francisco Varela from first- to second-generation networks: In search of the structure, dynamics and metadynamics of an organism-centered immune system," *Biological Research* 36 (2003): 25.

[60] For detailed explanations on the properties of dynamics and metadynamics, see the following articles. Francisco J. Varela and Antonio Coutinho, "Second generation immune networks," *Immunology Today* 12 (1991): 159-166; Antonio Coutinho, "A walk with Francisco Varela from first- to second-generation networks: In search of the structure, dynamics and metadynamics of an organism-centered immune system," *Biological Research* 36 (2003): 17-26; and John Stewart and Antonio Coutinho, "The Affirmation of Self: A New Perspective on the Immune System," *Artificial Life* 10 (2004): 261-276.

[61] Francisco J. Varela and Antonio Coutinho, "Second generation immune networks," *Immunology Today* 12 (1991): 159-166.

[62] Varela and Countinho, 159-166.

establishment of self-tolerance. The steps of the actually processes and mechanisms involved is well beyond the scope of this paper. However, suffice to say that, from the network standpoint of view, immune tolerance was the outcome of self-assertion. Varela elucidate further, "Self is what the system has learned to 'see' as self, and to discriminate from all other antigens that did not take part in its constitution."[63] In other words, contrary to Burnet's notion that immunity was the outcome of discriminating self from foreign, Varela argued that it was rooted in the ability of self-recognition. When immunologist John Stewart joined the group that had formed around Varela and Coutinho at the Pasteur Institute in Paris in 1988, they aimed to create an experimental model that would accommodate properties of metadynamics. As their discussions unfolded, it became increasingly apparent that computer simulations were the only possible alternative.[64]

Theories, metaphor, and research programs, the discipline of immunology witnessed the rise of two contending models in its history. In the era where global politics was ideologically divided between capitalism and communism, Frank Burnet's martial understanding struck a chord with both the scientific community and the general public. In the ensuing years, and truly up to the beginning of the twenty-first century, research programs were designed to verify immunity and the production of antibodies accordingly. On the other hand, Francisco Varela thought differently in the late 1970s. "Defense," he stated, "however, seems to be more of a side issue . . ."[65] Pivoting instead on the notion of self-determination, he articulated the theory of an organism-centered immune network that focused on the global cooperation and interconnectedness of its constitutive components. Given the fact that many of the South American countries and former colonies were fighting to establish their own path and identity,

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[63] Varela and Coutinho, 163.

[64] John Stewart and Antonio Coutinho, "The Affirmation of Self: A New Perspective on the Immune System," *Artificial Life* 10 (2004): 267.

[65] F. J. Varela and N. M. Vaz, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 257.

the political and cultural assumptions of Varela's perspective were equally as explicit as those embedded in Burnet's view. Experimentally, as Varela translated these characteristics into a research program that sought to preserve the whole of the organism, he challenged the conventional use of differential equations with computer simulations to study the network-like properties of the immune system. This approach also coincided with the broader revival of the importance of the organism in biological sciences. Lastly, perhaps it is only appropriate to conclude a section on the influence of scientific metaphors with this statement; that is, in the late 1970s, Varela demobilized the immune system that was militarized in the 1940s.

Francisco Varela and His Political Philosophy

In addition to the impact of Francisco Varela's work on theoretical immunology, interests in this new model also lie in how this peculiar definition of "self-determination" came to be the heart of his theory. Indeed, this question piqued the curiosity of historians and philosophers of science; and, to understand it, we need to interrogate the historical origin of this concept.[66] As I attempted to do so in this section, I sought to establish a few correlations. First, Varela's immune theory was an application of the theory of autopoiesis, which he had co-created with Humberto Maturana in the late 1960s. When his research focus switched briefly to immunology in the early 1970s, he saw appropriate to adopt it to make sense of the immune system. Second, the conception of autopoietic theory was in large part influenced by Varela's own philosophical thinking, which was forged as a result of his personal experiences of the political chaos in Chile in the late 1960s and the early 1970s. Therefore, I argue that his use of the network metaphor, with the intention to embody characteristics such as autonomy, individuality, and global cooperation and interconnection, was an effort to critique the political situation of the post-1954 era from the periphery.

The theory of autopoiesis stemmed from a 1960 paper titled "What the Frog's Eye Tells the Frog's Brain," which analyzed the activity of single fibers in the optic nerve of the frog.[67]

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[66] The most recent additions to the historiography are the following two books: John Protevi, *Political Affect: connecting the social and the somatic* (Minnesota: University of Minnesota Press, 2009); and Eden Medina, *Cybernetic Revolutionaries: Technology and Politics in Allende's Chile* (Cambridge: the MIT Press, 2011)

[67] J. Y. Lettvin, H. R. Maturana and W. S. McCulloch, "What the Frog's Eye Tells the Frog's Brain," *Proceedings of the IRE* 47 (1958): 1940-1951, in Mendeley, www.mendeley.com/research/frogs-eye-tells-frogs-brain-1 (accessed on January 20, 2011).

The theory of autopoiesis is sometimes referred to "second-wave cybernetics" or "cybernetics of the second-order" in the literature. The first wave began during World War Two when Norbert Wiener, John von Neumann, Claude Shannon, and Warren McCulloch formed an informal network that initiated the legendary Macy Conferences. Cybernetics is a science that studies the modes of control and patterns of communication in both the machine and the living system. Its principals have been widely used in many disciplines such as mathematics, engineering, the social sciences, and neuroscience. Researches by practitioners of cybernetics had led them to the concepts of feedback and self-regulation, and later on, to self-organization and self-reference.

Cybernetics of the first wave was devoted primarily to analyzing the technical problems of tracking and intercepting aircraft on grid system; and, as a result of this, related research projects were heftily funded by the military. However, this close association with wartime defense did not overshadow cyberneticists' initial intention to

This project was a joint initiative launched by a civilian institution, Bell Telephone Labs, and the US military - Army, Navy, and Air Force. It was believed that results derived from this project could be used in strategizing wartime maneuvers. In the conclusion, Lettvin, Maturana, and McCulloch explained their discovery, " . . . the eye speaks to the brain in a language already highly organized and interpreted, instead of transmitting some more or less accurate copy of the distribution of life on the receptors."[68] In other words, the means of communicating information from the external world to the internal was innate, and the phenomenon of knowing reality was the outcome of some pre-existing structure of organization.

From this discovery, Varela and Maturana - both of whom were neurophysiologists - made two important hypotheses less than a decade later.[69] They focused specifically on the mechanisms that brought about this communicative pathway. First, they claimed that the nervous system is a self-referential system, such that the perception of reality must be understood as a continuous creation of a new relation with the nervous system. Second, while interacting constantly with the environment, the components regulating this self-referential circularity are produced and organized by the system to maintain it.[70] Moreover, they contended that this type

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create a science of the mind. In essence, they asked the questions: "What is reality" and "How does the mind understand and interpret it in a meaningful way?"

At the core of their endeavour to answer how the mind shape reality was the difficult idea of self-reference with which participants of the Macy group struggled without much success. They believed it occurred as a result of a series of physio-mechanical processes. However, to discuss self-reference without resorting to psychoanalysis became one of the greatest challenges, as Norbert Wiener once proclaimed, "cybernetics is nothing if it is not mathematical." With World War Two approaching an end, the exigency to account for the lack of mathematical rigor that was in their explanations of self-reference was never satisfied before cybernetics lost its wartime glory.

Cyberneticists of the second wave solved this question a decade later with the discovery made in "What the Frog's Eye Tells the Frog's brain" paper. Drawing on the functional parallel between the amphibian and human visual systems, Varela and Maturana argued that what was true in frogs must also be in humans. In other words, they argued that "knowing reality" was a biological process instead. Or, as they stated in *Autopoiesis and Cognition*, "to live is to know."

[68] Lettvin, Maturana and McCulloch, 1950.

[69] Francisco Varela was not one of the original authors of the "What the Frog's Eye Tells the Frog's Brain" paper. However, he was under the tutelage of Maturana at the University of Chile, and the pair continued to work collaboratively on this subject.

[70] Varela and Maturana had in mind a very specific relationship that an organism has with its external world. They developed the notion of structural coupling. That is, a system is structurally coupled to perturbations of its environment, such that it continually reconfigures its components to accommodate these changes. The decision that

of self-organizing behaviour was a shared characteristic among all living systems.[71] In *Autopoiesis and Cognition*, Maturana and Varela stated, "It is this circularity of its organization that makes a living system a unit of interactions, and it is this circularity that it must maintain in order to remain a living system and to retain its identity through different interactions."[72] It was also to say that the resulting autonomy was foundational of life.[73] To encapsulate these concepts, they coined the term *autopoiesis* from the Greek words *auto*, meaning "self," and *poiein*, meaning "making."

Believing that there was a parallelism between how the nervous system and the immune system function, Varela used autopoietic theory to formulate the theoretical framework of an immune network. He borrowed principles such as self-organized circularity and the interconnection of parts to develop the key concept of self-reference. The resulting emergence of self-determination became a crucial quality to his model that was based on self and non-sense recognition. Furthermore, in *Self and Non-Sense*, Varela pointed out what he deemed as the ultimate purpose of immunity and the immune system. " . . . The more important issue [is] molecular identity," he stated, "of which the immune system is the essential regulator."[74] Be it immunological or organismal, it was the application of autopoietic theory that gave Varela the theoretical ground for such an emphasis on identity, as, according to it, the autonomy and individuality of a living system were always preserved.

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determines which perturbation should be acted upon is not random, according to them. Rather, it is the outcome of a series of cognitive decision-making processes. Varela and Maturana turned to the Santiago Theory of cognition to explain this aspect of the autopoietic theory.

[71] F. G. Varela, H. R. Maturana and R. Uribe, "Autopoiesis: the organization of living systems, its characterization and a model," *BioSystems* 5 (1974): 187-196; Humberto R. Maturana and Francisco J. Varela, *Autopoiesis and Cognition: the realization of the living* (Holland: D. Reidel Publishing Company, 1980).

[72] Humberto R. Maturana and Francisco J. Varela, *Autopoiesis and Cognition: the Realization of the Living* (Holland: D. Reidel Publishing Company, 1980): 9.

[73] Kepa Ruiz-Mirazo and Alvaro Moreno, "Basic Autonomy as a Fundamental Step in the Synthesis of Life," *Artificial Life* 10 (2004): 235-259.

[74] N. M. Vaz and F. J. Varela, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 257.

In the remaining section, I delve deeper into how these characteristics came to take such a firm root in Varela's thinking. In *Cybernetic Revolutionaries*, Eden Medina offered some insights into this by tracing the history of Project Cybersyn, which was a government initiative implemented by the Socialist president Salvador Allende in 1970. According to Medina, even though it was styled as an economic policy, its true aim was to fulfill socialism through bringing national industries under state control and developing policies to redistribute national wealth.[75] "[Project Cybersyn] was conceived as a real-time control system capable of collecting economic data throughout the nation," he explained, "transmitting it to the government, and combining it in ways that could assist government decision-making."[76] In other words, from a technological perspective, it utilized fully concepts of systems theory. As an umbrella discipline for autopoietic theory, and also for cybernetics, Maturana and Varela's work flourished under this encouraging climate established by the Allende government.

The broader political conditions notwithstanding, notions of autonomy, individuality and global cooperation that Varela emphasized repeatedly were convictions that were much more personal to Varela. His predilection for them was most evidently seen as stemming from his experiences of the political chaos in Chile. There were the dramatic seizure of power by General Augusto Pinochet, nation-wide institution of mandatory curfew by the government, and the brazen shooting on the streets by soldiers armed with submachine guns.[77] However, to Varela, none of which were remotely comparable to the loss of "[his] friends their lives, their torture, and the same for 80,000 or so people unknown to [him]."[78] The source I examined was the transcript of a speech titled "Reflections on the Chilean Civil War" given by Varela at the 1979 Lindisfarne

[75] Eden Medina, *Cybernetic Revolutionaries: Technology and Politics in Allende's Chile* (Cambridge: the MIT Press, 2011), x.
[76] Medina, x.
[77] Francisco Varela, "Reflections on the Chilean Civil War." In *Lindisfarne Letter 8: the Cultural Contradictions of Power*, ed. Gov. Edmund G. Brown, Jr., *et. al.* (the Lindisfarne Association, 1979): 19.
[78] Varela, 19.

Fellows Conference, with "The Cultural Contradictions of Power" as the conference subtitle.[79] By this time, Varela and his wife and a young daughter had already been in exile to the United States for a number of years.

Even though he did not seek to subvert the Pinochet regime openly in the speech, the message he delivered was nonetheless powerful and poignant. He stated:

> . . . [the Chilean Civil War] revealed to me the connection between the world view, political action and personal transformation . . . unless I was able to cut through my sense of identity and attachment and identification with what I believe are my ideas, my things, my territory, my limits, I had no hope of understanding what the hell was going on. And it literally turned my life inside out. What that experience told me was: "Unless you build on the foundation of working with that sense of spirituality . . . there is simply no hope of understanding" . . . I have found, for myself, expression of that understanding in Buddhist practice. I cannot separate that practice, that sense of working with the contemplation of how my mind and my actions generate and operate. I cannot separate that from political action and from what my understanding of the world is. I suppose this is why I become so passionate about issues on epistemology. Because epistemology does matter. As far as I am concerned, that civil war was caused by a wrong epistemology.[80]

From this statement, it was evident that establishment of an epistemology was important to Varela in two meaningful ways. First, as the world around him fell into ruin and as "we construct this world perspective with an epistemology," only a replacement whose purity that outmatched the destruction brought on by the Pinochet regime could disentangle Chile and the Chileans from this Gordian knot. Second, it was the foundation upon which everything concerning an individual was based. Therefore, the origins of his idealism and science, including autopoietic theory and its application to the immune system, arose from his epistemology.

It seemed Varela had always shown a proclivity for this topic. He was born in Chile on September 7, 1946, and died at the age of fifty-five on May 28, 2001 in Paris as a result of

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[79] Varela,13-19. Francisco Varela was appointed a Lindisfarne Fellow in 1977. In 1972, American writer William Irwin Thompson founded the Lindisfarne Association. His aim was to seek for new ways "to broaden the humanities by exploring the mystical roots of Western science and by bringing meditation into the thinking of philosophy and the practice of science and art." The William Irwin Thompson World Wide Web offers detailed information on the history of the association, http://www.williamirwinthompson.org/lindisfarne/history.html (accessed on 8 May, 2012).

[80] Varela, 19.

hepatitis C. He received his MSc in Biology in 1967 from the University of Chile in Santiago, where he studied with Humberto Maturana. In 1970, Varela received his doctoral degree in biology at the age of twenty-three from Harvard University under the auspice of the Paul Mazur Fellowship for graduate studies in the field of experimental biology. According to a tribute written by Evan Thompson, Varela's patriotism prompted him to return to Chile after graduation to help build a scientific community, for which he declined teaching and research positions offered by Harvard and another American university.[81] It was during the years between 1970 and 1973 that Varela and Maturana, now colleagues at the University of Chile, developed the theory of autopoiesis.

As Varela continued to pursue a dream "to study the role of mind in the universe," he published nine books and well over two hundred papers in research topics directly and tangentially related to the furthering of epistemology throughout his career. From experiments on the visual system of insects to mechanisms of sensory transduction in invertebrate mechanoreceptor, from science and technology of cognition and artificial intelligence to conversations with the Dalai Lama on Buddhist notions of the mind, Varela, like his mentor Maturana, strove to build epistemology by the way of understanding the biology of cognition.[82] Since his exile to the United States, Varela held positions at the University of Colorado Medical School (1974-1978) and the Brain Research Laboratories at the New York University Medical School (1979-1980), and was appointed Fondation de France Professor of Cognitive Science and

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[81] Evan Thompson, "Francisco J. Varela (1946-2001) - Tribute by Evan Thompson," *Journal of Conscious Studies* 8 (2001): 66.

[82] According to Evan Thompson's tribute, Varela was fond of telling the story of entering Maturana's office one day as an undergraduate student, informing him of his dream to want to study the role of mind in the universe. As the story went, Maturana responded, "My boy, you've come to the right place." Furthermore, in addition to *Autopoiesis and Cognition*, some examples of the more well-known book author or co-authored by Francisco Varela are H. Maturana and F. Varela, *The Tree of Knowledge: a new look at the biological roots of human understanding* (Boston: Shambhala/New Science Library, 1987), and F. Varela, E. Thompson and E. Rosch, *The Embodied Mind: cognitive science and human experience* (Cambridge: MIT Press, 1991). For information on Varela's complete bibliography, see Observer Web, http://www.enolagaia.com/Varela.html (accessed on October 13, 2011).

Epistemology at the Centre de Recherche en Epistémologie Appliquée (CREA) at the Ecole Polytechnique (1986-1991).

"Reflections on the Chilean Civil War" was perhaps the most candid speech given by Varela. It was also the first time he spoke publicly about the incident. "I can't really talk about the Civil War in Chile without being very personal," he stated, "And therefore, I am quite uneasy talking here today, because I haven't spoken publicly on this matter since those events, five years ago."[83] Despite being overwhelmed by these sentiments, Varela articulated a clear outline of what epistemology meant to him and the qualities it ought to possess. First, contrary to the conventional view that it was concerned only with the realm of abstractness, Varela argued that epistemology could be projected out such that "it creates the kind of world that we live in and the kind of human values that we have."[84] From political opinions to social mores, from personal convictions to moral values, it could be enacted upon to shape every aspect of our perceived reality.

Second, in doing so, Varela contended that the created reality was only one variant amongst many. "It is a relative frame," as he stated in "Reflections on the Chilean Civil War."[85] To illuminate this concept further, Varela referred to the set of circumstances that inspired him. When Salvador Allende became the first freely elected president in the history of Chile on September 4, 1970, his victory was greeted by rapturous celebration. However, according to Varela's recount, this joy was quickly dampened by the intense polarization of public opinions that divided Chile into two - between the Christian Democratic Party and the Marxist Party.[86] "It

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[83] Francisco Varela, "Reflections on the Chilean Civil War." In *Lindisfarne Letter 8: the Cultural Contradictions of Power*, ed. Gov. Edmund G. Brown, Jr., *et. al.* (the Lindisfarne Association, 1979): 13.
[84] Varela, 15.
[85] Varela, 16.
[86] Simon Collier and William F. Sater, *A History of Chile, 1808-2002* (Cambridge: Cambridge University Press, 2004), 303. In "Reflections on the Chilean Civil War," Varela referred to this political divide as the Polarity. Between 1964 and 1973, two reforming governments emerged. While they both attempted to implement structural changes to solve Chile's social problems and slow economic growth, the methods they each adopted differed

was absolutely and right down the middle a complete split," he reminisced.[87] "I cannot say that my political stance is true as opposed to yours, which is false," he continued, "But every political stance contains the elements on which the truth of the other is based, and that all we are doing is a little dance."[88] The political antagonism in Chile instilled in Varela the realization of perceiving things in relative rather than in absolute terms, a notion that later became integral to his epistemological framework.

By taking issue with one absolute reality, Varela in essence raised the possibility of viewing the world as a bricolage of epistemological projections that were relative to one another. A result of this controversial claim was the problematization of the process of knowing, especially with regards to the perception of reality. Consciously aware of the kind of theoretical questions this could lead, Varela proposed a crucial concept - the perspective of the describer - to account for this cognitive phenomenon. While the role of the observer was discussed at length in *Autopoiesis and Cognition*, Varela provided the term with a much more succinct explanation in "Reflections on the Chilean Civil War." Using the order of the energy of the universe that had been traditionally believed as an example of absolute concept, Varela contended that it in fact "depended on the system that is being described, and the describer that sees it."[89] In other words, according to Varela, reality was a perception charged with values that were subjectively imposed by the describer.

While reality was arbitrarily defined in Varela's epistemological framework, the inherent aim of the describer was undeviating. That is, it sought first and foremost to maintain the

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drastically. On the one hand, there was the Christian Democrats and their slogan of "revolution in liberty;" and, there was the Marxist party that believed in "transition to Socialism," on the other hand. During Allende's presidency, politics became ideologically charged, culminating to an intense polarization of public opinions. This led to the breakdown of the political system in September 1973, and the violent seizure of power by General Augusto Pinochet.

[87] Francisco Varela, "Reflections on the Chilean Civil War." In *Lindisfarne Letter 8: the Cultural Contradictions of Power*, ed. Gov. Edmund G. Brown, Jr., *et. al.* (the Lindisfarne Association, 1979): 16.

[88] Varela, 16.

[89] Varela, 14. In *Autopoiesis and Cognition*, Maturana and Varela used the term "the observer" instead.

autonomy and individuality of itself and, by extension, its sphere of interest. This was the underlying characteristic that united Varela's philosophical and political views and autopoietic theory, and from where the immune network theory derived its theoretical foundation. As Varela stated repeatedly in "Self and Non-Sense," the ultimate purpose of immunity was to preserve the identity of the organism against a constantly changing external environment. Further, this was also to say that the immune system configured its cellular constitution in accordance to the reality it perceived. In the case of immunology, this meant determining whether an antigen-induced perturbation was relevant to the self. This was the theoretical basis that formed Varela's immune concept of self-determination, and the essence that the metaphor of network intended to encapsulate.

In "Reflections on the Chilean Civil War," Varela's narrative shed insights into the shaping of the attributes of the describer. "Chile was, for me, a process of understanding, in the midst of a traumatic social transformation," he stated heavy-heartedly. In *Political Affect*, John Protevi recognized this impact as he investigated how our bodies, minds, and social settings are intimately connected. He developed the idea of political physiology, arguing that subjectivity-based reality was socially conditioned and "is [*sic*] sometimes bypassed in favor of a direct linkage between the social and the somatic.[90] With regards to coping with the political turmoil of the Allende government, and, later, the brutality of the Pinochet military dictatorship, Varela believed it was of paramount importance for the people to maintain their sense of self. He went further to suggest the strength to do so rested already deeply within what had made Chile as a nation and its people as an ethnic group unique. With a touch of pride Varela directed the attention of his audience to two contributing sources.

[90] John Protevi, *Political Affect: connecting the social and the somatic* (Minnesota: University of Minnesota Press, 2009), 61-112. In this book, Maturana and Varela's theory of autopoiesis and the history of its formation were used as an example in aiding Protevi's formulation of his theory.

In "Reflections on the Chilean Civil War," he first remarked on how Chile's peculiar landscape endowed its people with the distinct temperament that set them apart from the other South American regions:

> The fact that it is such a long country, going almost all the way from the Equator to the Antarctic, gives one the feeling of being in a long corridor. That gives the Chileans a character somewhat different from that of other South American peoples in the Inca-based countries (Peru, Bolivia, Ecuador) and very different from heavily European-influenced Argentinians [*sic*]. Chileans, by contrast, are very withdrawn - a somewhat melancholic people used to the rain and cold.[91]

In addition to the inseparable connection between the land and the people, Varela also praised the richness of Chilean culture in facing the challenges of other pervading forms of popular culture, foreign or indigenous:

> One of the most impressive things about the country is the Chileans' love for poetry. For some reason, everyone in Chile writes - or at least loves - poetry, and poets are the best national heroes. I have never been to a country where ten or twelve major poets are sold together with the porno magazines and Donald Duck.[92]

In Varela's mind, these innate qualities formed an unyielding foundation, upon which Chile and the Chileans could confidently draw to maintain their autonomy.

As he continued reminiscing, the intricate relation between Chile's political conditions and the formation of autopoietic theory became even more evident, and, similar to the interplay between Varela's immune theory and the metaphor of network, the influence was reciprocal. In particular, he pointed to the divide of public opinions between two political ideologies. "The polarity created a continual exaggeration of the sense of boundary and territoriality," he expressed.[93] Using consensus of print media such as newspapers as an example of how everyday life had been imbued with the effects of politics, Varela went further to explain, "You could go to the newsstands in the morning and one newspaper would say, "It's raining" and other would

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[91] Francisco Varela, "Reflections on the Chilean Civil War." In *Lindisfarne Letter 8: the Cultural Contradictions of Power*, ed. Gov. Edmund G. Brown, Jr., *et. al.* (the Lindisfarne Association, 1979): 15.
[92] Varela, 16.
[93] Varela, 16.

say, "It's not raining.""[94] With the reference to two distinct realities and the forming of a boundary, these seemingly inconsequential observations revealed the importance of maintaining autonomy. That is, it precluded potential clashes that would result in destruction on both sides. Furthermore, as the followers of one form of truth projected out their beliefs to create one reality, to safeguard this identity, they must winnow out any compromising information. The resulting effect was self-determination through self-relevance, for the whole of each own ideological camp.

An examination of the events that occurred during the years between the social and political unrest of the Allende government and the coup d'état by General Augusto Pinochet in 1973 completed an aspect of the evolution and development of Varela's immune theory I sought to present. The transformative power of this period in Varela's life left lasting and profound marks on his outlook on science and life, including even his religious and philosophical perspective. In the way that politics, his understanding of epistemology, and the conceptualization of autopoietic theory were interconnected, so were the application of the theory to immunology, the use of the network metaphor, and the computational modeling of the immune system. Therefore, this ongoing transition in theoretical immunology - from defense and attack to network - was not only driven by the mere necessity for more adequate scientific explanations, but was deeply rooted in culture, politics, and philosophy.

[94] Varela, 16.

Conclusion and Prospective Development

The SBPC meeting held in Brazil in 1982 had reverberating effects on a young science that was the field of immunology. When countries in the South American region fell in successions under military dictatorship, and when public opinions of dissension were highly oppressed, a major theoretical shift in science was slowly fomenting. At the meeting, Francisco Varela and a group of scientists and immunologists, including Nelson Vaz, Niels Jerne, John Stewart and his mentor Humberto Maturana, discussed the theory of autonomous immune network that he proposed in "Self and Non-Sense" three years earlier. Its aim was to explain immunological phenomena such as autoimmunity and immuno-diversity that were inadequately accounted for by Frank Burnet, who metaphorically described the immune system as a defense and attack system. As recent experiments have begun to show results affirming Varela's theory, many immunologists have come to agree that the discipline is undergoing a paradigm shift.

Contrary to Burnet's bi-polar construct of self versus non-self discrimination, Varela's immune network was concerned with the notion of self-determination. Its conceptual framework originated from the theory of autopoiesis, whose creators, mainly Francisco Varela, were greatly influenced by the events that occurred in Chile in the early 1970s. His experiences of both the political and social upheaval during the Allende government and the atrocity committed during the violent seizure of power by General Pinochet forged a political philosophy that emphasized strongly the importance of autonomy and individuality. In the post-1954 era, the same optimism was perhaps also his answer to a world that was torn by the ideological dichotomization between capitalism and communism and by the difficulties related to decolonization. Even though Varela was never politically outspoken in his life, the intention to offer a subtle critique was evident in "Reflections on the Chilean Civil War." When autopoietic theory became imbued with his ideals, and when its application was extended to immunology, Varela's worldview and science became one and the same.

Furthermore, the shift to computational modeling from the traditional method has since made profound impacts on not only the discipline of immunology. The abandonment of using tissue dissection and differential equations was to better assess the autonomous nature of an immune network, which, according to the principles of autopoietic theory, equated to the biological autonomy that defined life. This property had often been referred to as the emergence of the self, a characteristic that needed be considered as an irreducible whole.[95] To simulate it, Varela devised many radically novel experimental techniques.[96] In "Unbinding Biological Autonomy," Ezequiel A. Di Paolo termed these computational approaches collectively as simulation modeling, and expounded upon its other applications. He stated, "In short, the study of biological autonomy is perfectly suited for the work style of artificial life."[97] Niran Abbas similarly acknowledged this contribution by Varela in *Thinking Machines*. "Varela's theory is the discursive elaboration of Brooks' [*sic*] approach to constructing intelligent machines," he asserted.[98] In reviving the notion of the whole of the organism, Varela merged the study of life with computer technologies in the designing of a research program, thereby injecting a new perspective on the existing artificial intelligence research. This deep connection between the human body and mind to the machine was not surprising. Indeed, as the theory of autopoiesis has often been dubbed the second wave of cybernetics, Varela's work was already influenced by this

[95] John Searle, "Reductionism and the Irreducibility of Consciousness," in Mark A. Bedau and Paul Humphreys, eds., *Emergence: Contemporary Readings in Philosophy and Science* (Cambridge: the MIT Press, 2008), 69-80.
[96] N. M. Vaz and F. J. Varela, "Self and Non-Sense: an organism-centered approach to immunology," *Medical Hypotheses* 4 (1978): 248-250; Antonio Coutinho, "A walk with Francisco Varela from first- to second-generation networks: In search of the structure, dynamics and metadynamics of an organism-centered immune system," *Biological Research* 36 (2003): 159-166; and, F. G. Varela, H. R. Maturana and R. Uribe, "Autopoiesis: the organization of living systems, its characterization and a model," *BioSystems* 5 (1974): 187-196
[97] Ezequiel A. Di Paolo, "Unbinding Biological Autonomy: Francisco Varela's Contributions to Artificial Life," *Artificial Life* 10 (2004): 231-233.
[98] Niran B. Abbas, *Thinking Machine: discourses of artificial intelligence* (Hamburg: Cologne University Press, 2006), 130. In this statement, Abbas was referring to the roboticist Rodney Brooks, who contended that the "new AI" research of the 1980s, and onwards, was concerned with realizing autonomy. According to Abbas argument, Brooks' robots could be said to be the machine counterparts of Varela's theory.

branch of communicative science that thinks customarily in and through the algorithm of the computer.

In *Catalyzing Inquiry at the Interface of Computing and Biology*, a collaborative work published by the Committee on Frontiers at the Interface of Computing and Biology of the National Research Council, a speculative statement on the importance of biological autonomy to computing science and its future development was presented, "An important goal of computing is to be able to build systems that can function with high degrees on autonomy, . . . , configure themselves automatically into networks (and reconfigure themselves when parts are damaged and destroyed), . . . , learn from their environment with minimal human intervention, and "evolve" to become better adapted to what they are supposed to do."[99] Examples such as swarm intelligence and bacterium-inspired chemotaxis in robots were elaborated upon to indicate the power of biological inspiration. An area most pertinent to the topic of this paper is immunologically based approach to computer security, as the intrusion of pathogens to which the immune system must respond is comparable to some of the threats that computer systems encounter. In "Principles of a Computer Immune System," Anil Somayaji, Steven Hofmeyr, and Stephanie Forrest also believed that "immune systems have many features that are desirable for the imperfect, uncontrolled, and open environment in which most computers currently exist."[100] When relationship between organisms and antigens is no longer interpreted in a defense and attack framework, and when perception of external environment (reality) becomes subjectively defined by the organism's own constitution, architectures of computer security will also drastically change. Therefore, the theory of autopoiesis that Humberto Maturana and Francisco Varela created in the late 1960s and the early 1970s, which Varela applied to immunology in

[99] John C. Wooley and Herbert S. Lin, eds., *Catalyzing Inquiry at the Interface of Computing and Biology* (Washington, D. C.: the National Academic Press, 2004), 247.
[100] A. Somayaji, S. Hofmeyr, and S. Forrest, "Principles of a Computer Immune System," in *Proceedings of the 1997 Workshop on New Security Paradigms* (Landale: ACM Press, 1998), 75.

1979, is bringing about major theoretical transformations that are much more extensive than demobilizing the immune system.

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