History, Landscapes, Metaphors and Ghosts Around the Concept of Specificity

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The confusion between objects/processes and the language which describes them, leads to theories of doubtful verisimilitude about reality, inappropriate in time and even false, which distance us from the knowledge of perceived reality. In biology there are many examples of this kind of epistemological problem. Here we examine those related with specificity: a theoretical entity of enormous importance for biology and science in general. It sinks its roots beneath the evolutionary duality species-specificity, associated with the Linnean-Darwinist tradition that explains organized life in a discrete and hierarchical way. It conceptualizes the individual as an isolated agent fighting for survival as the foundation of a warrior vision of the immune system. Microorganisms are understood as inferior beings which should be eliminated in accordance with the self/not-self distinction. The use of these metaphors outside of historical context traces a map that guides the recognition of the Self and of the other according to the dialectic of Western biopolitics.

Keywords: Specificity, immune recognition, knowledge, metaphors, language.

1 Introduction

Language and reality: a changing reflection. The form in which an external reality exists in every human being is linguistic. When something becomes a part of our lives, when external reality exists for us, it is already internal and is rationally operated through linguistic expressions [1]: "the human spirit does not reflect the world but translates it through language" [2]. The meaning of words is not only in themselves, but also in their linguistic surroundings and in the temporal flow of that complex [1]. When attempting to express new realities, their translations into words face a serious obstacle: either they use already existent terms linked to “old” realities or they create new terms that are specifically coined but are explained by using the common language or metaphors, which are equally “old” [3].[1] Thus, a concatenation of metaphors is created which obscures the new reality by creating a familiarity that becomes confused with veracity [4]. Metaphors do much more than just lend old lexical meanings to new objects: they are literally ways whereby societies “build” webs of collective meaning and create cultural cosmologies of meaning-worlds which, once built, become the “homes” in which we reason and act, for better or for worse – places that constrain and determine our particular conclusions or actions [5].[2]

Cartesian subject-object duality supposes that there is an “outside” world, independent of perception, and proposes the scientific method as the verifiable way of knowing it. In many ways, perennial philosophy and other forms of traditional knowledge have constructed cosmogonies strongly contradicting the dualistic Cartesian vision; however, the dialogue between these and scientific thought has been closed for several centuries [6, 7]. Paradoxically, the advance of science has helped to show that through time things change and so does the capacity to perceive them, to express them linguistically and to react emotionally to them. Knowledge is not the product of an observation or a dual subject-object perception, but it strongly depends on the moment-to-moment relationship of the being and its knowledge [8, 9]: this has weakened the assumptions of the universality and immutability of scientific truth [2, 10, 11]. The conceptions of subject-object duality and “external reality” are again being questioned in various fields of science, including the microscopic world, the living world, the cognitive, the psychological, the social and the ecological [10, 12-18].

The confusion between objects/processes and the language which describes them, as well as the troubled reconstruction of the concepts based on it, leads to theories of doubtful verisimilitude about reality, inappropriate in time and even false, which distance us from the knowledge of perceived reality.[3]

In biology there are many examples of this kind of epistemological problems. Here we examine those related with *specificity*: a theoretical entity of enormous importance for biology. The concept of *specificity* is commonly used in many biological disciplines in which the reactions of association between a receptor and a ligand is an underlying factor, and yet, it is a presumably established concept, whose operation is obscure and incompletely explored. What happens is that biology and, in particular, immunology, have operated through metaphors regarding *specificity*, perhaps inadvertently.

We have assumed the task of examining the currents of thought or paradigms that have directly or indirectly influenced the establishment of the concept of *specificity*. We pose the exploration of the main hypotheses which have explained it since the beginning of the 20th century up to the present, in the hope of identifying the ideas that have given meaning to the concept, as well as their implications for the scenarios of immunology. From the systemic ideas that some of the first researchers of *specificity* outlined, we seek to join up these proposals with the recent evidence regarding the context of *specificity*. Likewise, we reflect on other biological phenomena which are based on the receptor/ligand reaction.

Since the difficulty in defining *specificity* involves not only an observational problem but also an epistemological one, in this essay we attempt to reflect on both problems. This will imply approaching the complexity of the natural phenomenon and its explanation considering the sociological settings in which science develops [16, 17]. For a closer approach the complexity of this problematic we have decided to write a text with at least two parallel lines of reflection, which will allow us a more complex argumentation. In this way we supply the reader of this essay with some footnotes that lateralize the issues of the main text.

2 What are the Importance and the Limits of *Specificity*?

A great number of biological phenomena occur after the reaction of association of a receptor with a ligand. The properties of the reaction are habitually studied within the context of the Mass Action Law: “At constant temperature and pressure, the rate of a chemical reaction is directly proportional to the product of the effective concentrations of each participating molecule.” Some examples of these reactions are:

enzyme-substrate, antigen-antibody, hormone-receptor, neurotransmitter-receptor and hemoglobin-oxygen. All demand certain "*specificity*" between the subsystems (reactants) involved in each one of them, that is, they demand that the reaction occurs with a limited number and type of the different possible reactants present in the environment.

From this perspective, the *specificity* of a reaction limits the operativeness and the connectivity of each molecule before a set of enormously diverse options, from which, however, the molecule is able only to recognize what corresponds to it, since the rest has no specific significance [19]. The concept of *specificity* has been considered as the key to ordered physiology, for a healthy life and to the reproduction of life, which implies that its violations lead to illness and extinction: *The cemetery of unspecific beings must be innumerable.* Parallel to this, *specificity* may be understood as a state of a transitory process in which an organism passes from disharmony to harmony with the context, as Mechnikoff expressed it:

> "*An archaic phylogenic structure present at any stage of ontogenic development not only precedes but also must coexist with new structures. Thus arises a requirement not only for an accelerating mechanism of development but also for a harmonizing constraint. An active mechanism then is required for harmonizing the coexistence of structures of different phylogenic origins. In a broad sense, the mechanism must harmonize apparent disharmonious inherited structures*" [20].

Specificity is thus a matter of great importance in biology. Some ligands may have a wide range of specificities: for instance, they can be at the same time substrate, antigen, hormone and neurotransmitter. But their functional identity depends on their associations (enzymes, antibodies, membrane receptor, etc.). Unlike the receptors whose functions are more limited: the ligands are generally not enzymes, or operators of neuronal networks. *Specificity*, then, depends not only on the chemical structure of the reactant molecules and much less on only the composition and the chemical structure of the receptor, but also on the structural characteristics of both molecules [21], on the conformational state (molecular pre-stress) of the ligand-receptor [22], on the connectivity of the ligand-receptor with each other [23] and with the environment [24], as well as on the observer's conceptual and experimental framework [15, 25, 26].

The last ambit, that is, the role played by the observer and his/her ideas, has not received the attention it deserves, since *specificity* is generally assumed to be an "objective" fact of nature. Nevertheless, discoveries are not only objective entities, but also depend on the context and on the observer. For instance, they participate in the personal history (illness as a divine misfortune or as a result of material processes depending on the religious or rationalistic environment in which that particular person had lived), the set of current experimental and logical criteria for the validation of an observation or explanation, the social position of the researcher (the differential weight of an affirmation stated by a Nobel Prize winner or by a student), the state of the scientific knowledge contemporary with the discoveries (the dominant paradigms), etc. [27, 28]. In agreement with the foregoing, Fleck states that: "scientific facts' do not exist 'out there', simply waiting to be discovered by objective, interchangeable observers; they are produced by distinct thought-collectives, each composed of individuals who share a particular thought-style, incommensurable with that of other thought-collectives" [29].

3 Origin of the Term *Specificity*: the "Mental Landscapes" and the Fight for the Highest Bidder

The concept of *specificity* appears in biology in an effort to order living things in groups (species) which share a high number of phenotypic characteristics (now genotypic) that distinguish them from the rest of living things. The bio-philosophical position regarding the degree of distinction among the groups or sets of organisms poses a dilemma[4]: the point of view or the discrete mental landscape defines species as sets of organisms clearly isolated from one another; whereas the *continuous* landscape defines only one conglomerate of individuals with similar or diverse nuclei having evanescent limits, which is called biomass [30, 31]. According to the foregoing, the specificity of certain attribute describes its exclusiveness to a limited group of individuals and refers to attributes that are directly dependent on the material residing in the object. For the discrete landscape, specificity is a quality of things and *specific* is an adjective which is applied to a thing or set of things with a high degree of exclusiveness. For the continuous landscape, specificity is a quality that arises from the relationship of individuals with their environment and is distributed, with distinct probabilities, among all living things.

Ever since Linneaus proposed his first classification of plants, the terms *species* and *specificity* have been the object of great debate. Lamarck questions Linneaus, affirming that the division of the biomass in classes, orders, families and genera are artifacts of psychological devices introduced by humans because of the convenience of simplifying in order to understand [32]. Biomass, according to Lamarckism or neo-Lamarckism, is really a continuum in which intra-organismic barriers lack rigidity and the environment plays a central role in its evolution. In spite of Lamarck, Darwinism and neo-Darwinism, with their natural selection of species, have historically dominated the theory of evolution. The supremacy of Darwinism had a great impact on the establishment and settling of the terms *species* and *specificity*, which are freely applied in particular disciplines and at different levels of organization to set up a logic of interrelations in discontinuous systems. For example, since evolution and Darwinian selection affirmed that species differ in degrees of organization and are in constant competition and conflict, microorganisms were placed into an evolutionarily inferior and potentially harmful category. This posture was adopted in Koch's works through the specific association of microorganisms with illness, and later by immunology in viewing the immune system as a defensive tool used by vertebrates against inferior beings [30, 33]. For infectology, this means that microorganisms pass to the category of enemies and justifies their destruction through powerful and lethal antibiotic principles [34].

The generation of knowledge is not linear as it is thought to be; the "old" vices, virtues and cultural beliefs are frequently dragged alone and integrated under the innovation that homogenizes[5] [27, 35, 36]. These rigid distinctions of microorganisms as species filtered into medicine by suggesting a specific and univocal relationship between causal agents and different illnesses.

Only now, with the most recent advances in biomedicine such as the sequencing of genomes, epigenetic processes, pleomorphism and the horizontal transference of genes, etcetera, is the discussion on Darwinism, neo-Lamarkism, epigenesis and other important topics regarding the continuous and discrete character of the biomass: *specificity*, coming back to life [37-39]. Darwinism has become weakened and Lamarck's ideas are starting to be revalued, although they are still considered suspicious by "normal" science. Lynn Margulis and his symbiotic theory have occupied a central place in this debate. This theory affirms that there are no superior or inferior organisms, since all living things are equally evolved; to the struggle for survival, cooperation and co-evolution are added, and the artificial limits for defining species are strongly questioned [34]. Additionally, these and other findings establish bonds, previously unsuspected, among viruses, bacteria, plants and animals, and they have strengthened the posing of theories including the process of global and planetary organization [40-45].

The foregoing is supported by a diversity of evidence showing that various species of microorganisms live in community, where they share a common place and have similar and or complementary metabolic characteristics and trophic needs. The degree of organization of these microbial communities is such that they have been considered as multicellular organisms, since they show communicative and decision-taking skills which allow them to coordinate their growth, movement and biochemical activities. Each individual cell of the community is able to receive, interpret and respond to information from its neighbors. Furthermore, this co-constructed information is at the same time environment and memory which co-determine a pre-pattern of organization and collective functioning [46-48]. According to Margulis, evolving creativity cannot be understood only by considering the classical processes of Darwinist evolution, since cooperative and symbiotic strengths among groups of organisms allow the co-creation of organization, which is highly pertinent for evolution [34, 49, 50]. This complex global integration is the result of the symbiotic and or co-evolving interaction among the fitness landscapes of the living things that form it [34, 49, 50]. Microbes and human beings, in fact all living things, are linked through functional networks, and these networks at the same time promote diversity, adaptation and co-evolution [34, 41, 47, 48].

In this co-evolving process, the movements of an organism deform the fitness landscapes of other organisms [51-53]. The environment plays the role of a disturbing agent, but at the same time it is disturbed. Structural changes in individual organisms are neither determined nor exclusively instructed by the environment; instead, they are parts of a complex interactive network in which evolutionary history (or natural drift) is a result of mutual structural changes between the living thing and the environment [8]: of an Auto-Eco-Organization[6] [15]. These changes are unchained by the disturbing agent and are determined by the structure of what is disturbed [8]. This point of view is very far from the mental landscape constructed by neo-Darwinism in which the genetic material (DNA and RNA) is the only one able to control, codify and inherit the essential information of a living organism, and the environment only operates to shape the limits and details of the organism. Such a vision was supported in part by the premise that organisms are distinct autonomous units with fixed limits. However, this opinion about the organism has been debated and progressively enriched with a more dynamic vision of the organism, in which it is conceived as an articulated and interactive unit.

Infectious illnesses are a specific case of changes within a constellation of parts that reciprocally act in the living unit. Those changes should be compared with the reaction of ions in a solution, something more than just a battle between two hostile armies.

> "*It is very doubtful whether an invasion in the old sense is possible, involving as it does an interference by completely foreign organisms in natural conditions. A completely foreign organism could find no receptors capable of reaction and thus could not generate a biological process. It is therefore better to speak of the complicated revolution within a complex life-unit than of an invasion of it*" [25].

An organism can no longer be considered as an autonomous, independent unit with fixed limits, as the epistemology of materialism-mechanisms still considers it. The concept is an abstract tool and is permanently in conflict, and its particular meaning depends on the purpose and the context of the research. Corresponding, the history of concepts in immunology, and in particular regarding the *specificity* of the immune reaction, reveals an intricate network of implications constructed mainly from the personal and social conditions of the participating actors [26, 28-30, 33, 54-59].

In physiology, we find the concept "harmonious unit of life," according to Gradmann: "characterized by the notion that the activities of the parts are mutually complementary, mutually dependent upon each other, and form a viable whole through their cooperation" [29]. The complex vision of life proposes that the information resides in the dynamics (epigenesis) of the metabolism and functioning of the cell and the organism in their totality and, furthermore, in the relationships between the organism and the environment and in general with the planetary environment [60, 61]. On this symbiotic planet, bacteria and viruses (and all living things) are protagonists of life and evolution and not only causal agents of illness or biological machines for producing of food and drugs for humans [34].

4 *Specificity* and Immunology

Immunology does not escape from the flights of fancy in the discussion about the organization of living things, which are grouped within precise and continuous limits. For instance, in 1967 Niels Jerne proposed that there were two kinds of immunologists: the "trans-immunologists" who concentrated more on the chemical aspects of the immune-response and on the molecular bases of immunological *specificity*, that is, this group was interested in the structure of the antibody's molecule and its binding to the antigen. On the other hand, the "cis-immunologists", who were mainly biologists, were interested in the effects of antigenic exposure and the functional character of the immunological response, as well as in its immune-biological and evolutionary implications [29, 57]. According to the foregoing, a cis-immunologist could hardly communicate with a trans-immunologist, not only because the objects they studied were different (as Jerne posed it), but because they saw the same process in a different way (and sometimes irreconcilable) [29]. However, the growing acceptance of the clonal theory for explaining the synthesis of antibodies, on the one hand, and the progress in understanding the mechanism of proteic synthesis and the role of cellular receptors in the regulation of immune phenomena, on the other, reduced the distance between the cis- and the trans-immunologists. We believe that their gradual integration led to the clarification of the main mechanisms responsible for the synthesis of antibodies, but also to the reduction of the "Self" and, therefore, of the phenomenon of recognition to a static molecular archetype. Thus, genetic-molecular immunology became the almost universally prevailing paradigm, discrediting systemic immunology (adhering to the notion of auto-eco-organization), an immunology that is still struggling to be heard [29].

The tendency toward the validation of the biological concept of *specificity*, gives rise to the construction of the immunological concept of *specificity*: the capacity of immunological discerning among distinct antigens. This property endows vertebrates with the capacity for distinguishing (more exquisitely than other living things) between Self and Non-Self, between dangerous and harmless, among individuals or among species [62-65].

Contrary to Burnet's "Self" theory, which overestimated the importance of hereditary factors in the recognition of "Self/Non-Self," Jerne's theory promoted the "humoral personality", that is, the impact of the individual's history on his/her immune-response. According to this theory, immune systems were developed not only for preserving the organism's integrity (discrimination between "Self-and-Non-Self"), but also its evolution was the result of "getting to know oneself." Before the cells of the immune system encounter the antigen, they need "to talk" among one another; thus the immune-response is regulated through a network of responses previously constructed by means of an internal dialogue [29, 66-69].

Therefore, seen from the other limit, the proposals on the global articulation of organisms and communities and other particular theories like that of the immune network, put the interpretation of immunological *specificity*, understood as an exclusively defensive weapon against invaders or dangerous fifth columnists to the test [69-71]. From the systemic point of view, the immune system is seen as a not necessarily bellicose interlocuting agent between the parts constituting an organism, as well as between organisms and environment.

Haraway, emphasizing the social condition of knowledge, poses the immune system as "an elaborate icon for the principal systems of symbolic and material 'difference' in late capitalism" – in particular, it is "a map drawn to guide recognition and misrecognition of Self and other in the dialectics of Western biopolitcs" [72]. That is, the immune system is a meaningful action plan that constructs and maintains the limits between Self and Non-Self within the territory of the normal and the pathological [29, 57]. This biomedical discourse provides us with an organized body as a directed communication system, ordered by a fluid and disperse "intelligence-command-control" network.

Emily Martin, from a different perspective, proposes that: "the Self has retreated inside the body, is a witness of itself, a tiny figure in a cosmic landscape, which is the body" and conclude that "the science of immunology is helping to render a kind of aesthetic or architecture for our bodies that captures some of the essential features of flexible accumulation" [57, 73]. This would reflect a highly dynamic, systemic vision of biology, in which the Self arises from complex cellular "learning" and "communication", that is, "Self" in this regard becomes an interactive concept (Selfhood); its manifestation as immune processes fundamentally parallels matters of the mind in which immunity not only defines the host/organism/individuality, but also defines that entity [58]. The realization of the Self is determined in the complex duality of its own self-consciousness, which is intimately dependent on its relation to the other – whether it be God, nature, culture, history, or other selves [33].

Thus, a very different point of view implying a diplomatic order of immunological physiology has been created, and it coordinates individual interests with the global ones of living things: an alternative perspective to that represented by military metaphors between hostile nations, in which the invaders of an organism are considered as a threat to its life and/or identity and are attacked by molecular and/or cellular weapons. As Moulin has posed: "the immune system was a kind of metaphor, but ecumenical one. It solved the need for communication not only between cells, but also between professionals of immunity" [74]. The foregoing makes it evidence that knowledge is temporarily tied to space in a recursive context in which views regarding the nature of immunological *specificity* create the observational conditions that support explanations and worlds. These explanations and worlds co-determine and, at the same time, are contextualized in a social landscape, a landscape that produces immunologists.[7]

This perspective made it possible to adopt social metaphors like *Self/Non-Self* and *dangerous/harmless* as the immunological function, orchestrated by families of molecules (antigens/antibodies, antigens/MHC T-cell receptors) whose interaction leads to subsequent biological processes of acceptation/estrangement or health/illness. Under this repressive scheme of the immune system, the iso-antigens represent a unique "Self"- identity card and the alo-antigens represent the passport of the citizens of a certain country, whereas the antibodies correspond to the lists of individual or civil registration. All these entities and concepts situated in a condition of certain unequivocal meaning (reactivity structurally determined in the molecule itself) is a property consistent with the notion of an immune-genetic program (see the next section) a bunch of metaphors seductively congruent with its Darwinian origins of species and at the same time suspiciously anthropomorphic. Through the 1940s, the immune system was generally regarded as a system of defense, but it had to wait for the postwar period to expand immunology's domain with immune surveillance of the host itself. During the first decades of immunology, many of these epistemological and ontological questions concerning the immunological phenomenon were the object of open debate among authors and schools of thought (Gruber, Bordet, Fleck, Landsteiner, Koch, Ehrlich, Burnet, between others) [29, 30, 33, 55-57, 59]. However, the winning opinions were later imposed as hidden metaphors; consequently the living reflection about the problems was not incorporated into the mainstream of immune theorizing and experimental programs [33]. The concepts of Self and Non-Self provoke a generally understood message, an implicit pronouncement that immunology deals with distinguishing the organism from its world, but emphasis is placed on the mechanisms, not on the entity [58].

5 The Antigen-Antibody Reaction: the Molecular Archetype of *Specificity*

Immunological *specificity* appears at various levels of biological organization (molecular, cellular, individual and populational), but the reductionist tradition assumes that all the specificities which manifest themselves in other settings (the specificity of vaccines, of diagnostic methodologies, of cellular communication, among others) are at the molecular level. The predominant present theories have been elaborated from the *specificity* of the interaction between antigen (Ag) and antibody (Ab) molecules, these theories explain the origin and nature of the diversity and functioning of the immune system. Given the technical facilities derived therefrom, at the end of the dispute, the known properties of the Ag-Ab reaction became the archetype of the reactions between receptors and ligands in other physiological settings, notwithstanding that around 1900 there were two currents of thought in physiology that contributed to the interpretation of the Ag-Ab reaction.

In the first case, the interpretation was based on organic chemistry principles, which can be traced to Edward Pflüger's idea that the cellular substance consisted of a huge albumin molecule in which chemical compounds were formed and destroyed while the cellular substance was alive. In the other case, the interpretation of the Ag-Ab reaction was supported by the physical-chemical characteristics of living matter, which were being investigated by the new methods of colloidal chemistry. This physicalist school followed Thomas Graham, who in 1861 distinguished between the crystalloids, typical of the inorganic world, and the colloids, whose peculiar physical characteristics and chemical inertia made them the elements of life [54]. Though the two currents offered systemic and complex ambits, it was the ankylosing of the contextual, organizational and systemic factors and their consequent subordination to purely material considerations (the two groups agreed on the central importance of proteins in their schemes of thought) that reduced the process of recognition to a rigid *key-lock* model, as we will see later on.

Koch's perspective of discontinuity and separation among bacterial species, which implied a relationship of one to one, or specific, between the microorganism and the infectious illness, was not only transferred to the context of the Abs and Ags; it also introduced within the notion that *specificity* was no longer a gradual matter [30, 75]. Within the framework of this mental landscape, Ehrlich proposed his famous "side chain theory" of the formation of antibodies, which is based on an analogy between the iconography of benzene molecules and the cell, the latter being a kind of giant molecule with a ring of benzene in the core (which corresponds to protoplasm) and chains of atoms (interpreted as "side-chains" or, later on, "receptors") extending outward from the central ring (protoplasm) [26], that is, the cell itself was conceived as a rigid structure. This theory in turn gave birth to the chemical-static metaphor of *key-lock* for the enzymes and receptors, which matches a type of Ab with each type of Ag, and in which there is an absolute *specificity.* This means that a particular "side-chain" or "receptor" may or may not react at all with some given "poison" or "toxin", as a result of the presence or absence of mutually adjusted chemical groups [26]. Ehrlich proposed that … "When an organic fluid manifests a particular property, it is always the case that it owes this property to a material agent." Every vital process – specific vital activity, reproduction, assimilation, growth, multiplication, perception, thought, will – is the work of the cellular substance… the expression of a chemical organization… [54]. However, Bordet attacked Ehrlich's proposal, postulating that it was "irrational" to assume the existence of a given (fixed, narrow) characteristic, that endows an antibody with particular atomic groupings inscribed in its molecule [26]. According to the foregoing, Bordet had opted for a more diffuse mechanism, postulating that the "agglutination" was due to the complex and contextual interaction among all the substances present in the solution [26].

The difference between both perspectives was then in the way of conceiving the essence of the biological effect and its relationship with the molecular level, that is, between the complex articulation among diverse molecules and circumstances or a simple and pre-determined interaction of the Ag-Ab complex; more specifically, the difference between the strong bonds of organic chemistry and the weak ionic bonds of electro-chemistry. This is because Ehrlich's emphasis was on the firm chemical binding between antigen and antibody (a covalent type of bond), whereas according to Bordet's opinion, the antigen-antibody binding represented a weaker and physical (colloidal) interaction. The problem of distinguishing between strong and weak bonds permeated the discussions that followed about immunological specificity and its phenomenological consequences [55]. In regard to this, Bordet argues that Ehrlich's posture implies turning "words" into a "phenomenon" by simply naming molecular types. He does not challenge Ehrlich's emphasis on *specificity* (which Bordet himself recognizes as "the most obscure and important question"), but he vigorously rejects the idea that *specificity*, by itself, is the expression of properties of molecular configuration of the antibody or of the antigen-antibody interaction [59]. In addition to this, Bordet criticizes Ehrlich for ignoring that the qualities of the antigen have a marked effect on the antigen-antibody binding, that is, the classification of the phenomena should be based not only on the antibody's characteristics, but also on "the antigen's." This suggests that all the antibodies are similar but their effects vary according to the antigen encountered [59]; the Ag-Ab reaction is relational [23], the *key-lock* can not be considered as the archetype of all the facets of the implicated processes.

Gruber, as Bordet, stirs controversy against Koch and Ehrlich's vision of *specificity.* He argues that a single antibody can interact, through gradual affinities, with a great diversity of antigens, that is, an antibody can react with a great variety of related antigens, not necessarily identical, which makes the *specificity* of the serum an expression of the degrees of affinity in the binding (which reaches its maximum with certain combinations), this being a much broader conception than that admitted by Ehrlich's theory of a simple and absolute specificity [56]. Gruber's position was inherited by his student, Landsteiner, who finds Ehrlich's opinion a little bit uneconomical. He thinks that such a hypothesis implies the presence of a great amount of specific substances (Ab) in the serum, requiring as many substances as Ags on nature [30]. Landsteiner proposes a simpler vision in which the diverse antibodies are not determined beforehand as specific, but that all (or at least many) react with different affinity with diverse Ags, following the rules dictated by the composition of their chemical structure. Besides, Landsteiner developed the theory of the colloid of immunology, in which the reactions are influenced by the chemical constitution of the substances, but above all, the quantitative relationship is influenced by physical phenomena such as solubility and temperature [28]. The antibodies' reactions, says Landsteiner, seem to be chemical in their individuality but physical in their quantitative aspects:

> "*It appears that in the living organism these peculiar reactions play a particularly important role, and that the combination of colloid, which form a larger part of the living substance often follow no fixed proportions … on these grounds then, the protoplasmic substance cannot be seen as a definite compound of which the constitution can be shown by the valency theory. The*

> *order point of view seems more likely, in which this substance is seen as a system of which the parts have variable, not fixed relationship to each other ...*" [54].

The colloid is, in fact, a dynamic state of matter and the crystalloid, the static condition. The colloid can be seen as the probable primary source of power that appears in the phenomena of vitality. The colloids also have the characteristic of precipitating when the physical characteristics of the solution, such as the ionic content, change [54].

Although Landsteiner's vision is much broader and contextual than Ehrlich's, the different mental landscapes of the time are not absolutely discrete nor excluding[8] [27, 36]; for that reason and parallel to the discrepancies in their theories, these and other authors shared an exclusively chemical and isolationist point of view of the Ag-Ab interaction.

The point of view of the complete system that joined colloid proteins and life completely disappeared from the biological sciences, since the old premise of Ehrlich regarding one-to-one specificity remained essentially without changes [28, 54]. In fact, Landsteiner's empathy with the colloidal interpretation did not survive the decade (from 1903 to 1912), since he relinquished his "physical" position in favor of a more chemical one, although he never stopped arguing against the absolute *specificity* of Ehrlich [56].

Then Pauling proposed that the Abs adjust themselves here and now to the Ag that they confront, the Ag serving them also as a pattern or instructor for their spatial configuration. In his classical book "*The Specificity of Serological Reactions*", Landsteiner comments on Pauling's instructionist theory as follows: "*it is assumed that antibodies differ from normal serum globulins only in the way in which the two end parts of the globulin polypeptide chain are coiled, these parts, as a result of their amino acid composition and order, having accessible a very great many configurations with nearly the same stability; under the influence of an antigen molecule they assume configurations complementary to surface regions of the antigen, thus forming two active ends*" [76]. We might add that not only under the influence of the antigen, but also and fundamentally, under the influence of the reaction environment (see below), the conformation and the reactive properties of the "*anti-corpus*" are co-determined.

From our point of view, this reflection may have diverse readings, although the principal reading provided by the history of immunology in with respect to the strict instructionist character of the formation of antibodies, that is, the antigens are the pattern directing the formation of the antibody. However, we consider that a new reading of this proposal in other directions, above all in the light of the historical retrospection we have made herein and that of other authors [26, 28-30, 54-56], allows compatibility among many of the problems regarding the concept of *specificity* dealt with in the present work [77]. For example, Ludwik Fleck in his famous book *Genesis and Development of a Scientific Fact* compared "antitoxins" with "states" rather than with "substances chemically defined" [25, 26], that is, he proposed speaking of states or structures rather than of substances. From this perspective it is possible to propose that a complex "chemical-physical-morphological" state is responsible for the changing mode of the reaction, instead of the chemically defined substances or their mixtures being, the cause [26]. In fact, Fleck was being influenced by the discoveries made in physics[9] when he postulated that the conception of "antigens" and "antibodies" should be replaced by the principle of colloidal chemistry and of the physical forces (fields) that modulate biological reactions [29]. Actually, we do not know whether, before the start of the immunization process, antibodies are specific molecular aggregates or simply physical forces depending on the altered superficial energy of the same substances present in the blood [26].

The contributions made by Landsteiner and Pauling to the understanding of the biochemical bases of *specificity* were transcendental, but at the same time profoundly controversial [78]. On the one hand, these authors made the chemical requisite of *specificity* more complex upon adding geometrical requirements of complementarity in the reactant molecules [79]. This geometrical complementarity permits some proximity between chemical groups so that the interaction is energetically meaningful. Simultaneously, these chemical groups in confrontation at appropriate distances should be complementary. The second great implication of Landsteiner and Pauling's proposal tended toward a flexible and malleable vision of the antigen binding site. This perspective was accepted only for a few years, and then was violently rejected and ridiculed. This rejection, on the one hand, was based on the fact that this perspective apparently violated the primordial principle of proteins folding, and on the other, on its implication that with only one gene of immunoglobulin the whole problem of the diverse specificities of the immune system could be solved. Plenty of evidence contradicting these affirmations appeared in the 60's and 70's [79]. **In our opinion, the tragedy implicit in the rejection of the instructionist hypothesis is that it carried away in its discredit not only the vision that it was the antigen that "guided" the antibody in the construction of its specificity, but it also totally discredited the flexible and contextual vision of the specificity phenomenon.**

The triumphant perspective was the one summarized by the model that enabled Tonegawa [80] to obtain the Nobel prize in 1983 by explaining the specificity of Abs through the structural diversity of immunoglobulins (Igs); this in turn was built within a genetic-molecular not cognitive "Self", the product of the epistemological constructions of clonal selection that we have commented before. In other words, after 1941 the "Self" coined by Burnet, with a profound psychological Freudian background, in which the cells were internally harmonized enzymatically, would change as a consequence of the closer relationship of the abstract model of the "Self" with the genetic individuality. In the latter sense of genetic reductionism, Burnet even postulated the one-to-one "gene-antigen" relationship [58]. Thus, through Ehrlich, Burnet and Tonegawa, the dialectical history between chemists and biologists (the cis-and trans-immunologists) was to be solved to give birth to this profoundly confirmed perspective stating that the diversity of antibodies is a result of the diversification the germline genes of Igs and that it is increased by processes of mutation and mechanisms of diversification in somatic cells [57, 80]. This not only placed the source of diversity into a linear authoritarian and selfish genetic program, but also made the antibodies rigid entities participating in specific molecular interactions predetermined and disconnected from a context, that is, the experiential content was taken out of the recognition phenomenon. This occurred even though at the end of the 40's Burnet and Fenner reverted the perspective of the "Self" to a cellular-ecological model in the second edition of their book *The Production of Antibodies* [58].

In order to clarify that throughout history all these mental landscapes have perturbed those that follow in their origins and conceptualization, we have tried to capture this process in an esthetic way (Fig. 1).

Figure 1: "Perturbantes Paradigmas Paralelos" (Parallel Perturbing Paradigms) depicts the perturbations of the affinity constant (K) by other paradigms of different colors as they flow through time, from left to right.

6 The Key-Lock Metaphor

Specificity at the molecular level is a highly contradictory concept. On the one hand, it creates a sense of security in people who use it, since it seems to be solidly based on structural biochemical evidence, which postulates a rigid *key-lock* model. On the other, it is a vague concept, without definition, that is explained through metaphors.

Let us see what Fred Karush, one of the few immunologists that have been interested in the history of their discipline, says about metaphors: "... they are vehicles for formulating the most basic concepts... they associate with human experiences of a biological and cultural nature in another context or setting.... they name or characterize a new phenomenon or idea through references to concepts with which one is already familiarized, thus they cause the sensation of understanding a phenomenon through explanations of another, giving the idea that it is a settled matter" [4]. Or as Kuhn said: "Metaphors play an essential role in establishing links between scientific language and the world. Those links, however, are not given once and for all. Theory changes with changes in some of the relevant metaphors and in the corresponding parts of the networks of the similarities through which terms attach to nature" [27].

The prevailing metaphor of immunological *specificity* at the molecular level is, now and of course, that of the key-lock. This is because in the mental landscape of immunochemistry, the perspective of the last hundred years has always referred to a chemical and geometrical molecular complementarity between the Ag and Ab, in spite of the existence of parallel discourses that have complemented it, as is the case of the colloid theory. The basic dispute as to whether the *key-lock* is rigid or adjustable does not question the nature of the isolationist-mechanist perspective which deposits all the relevant information for *specificity* in the structure of interacting molecules [81]. Unfortunately, during most of the 20th century, alternative systemic perspectives about the nature of the biological processes were ignored [51, 60, 82]. Particularly in this respect, we can cite the work of the Polish school of medical philosophy and the proposals of Fleck that have been reviewed here, proposals that supported and deepened the contextual perspective of Gruber and Bordet. These kinds of perspectives have been ignored almost totally by established immunology.

On the other hand, regarding the origin of Abs (locks), two predominant versions have historically existed: the lock is pre-made, according to Ehrlich, or is made instantly, according to Pauling and later Landsteiner in the instructionist model [79]. For both versions, the stability of the Ag-Ab binding is maintained by the sum of relatively weak forces, in which hydrogen bonds, electrostatic forces and hydrophobic interaction predominate [78]. In the history of immunology, Landsteiner's version of chemical complementarity, integrated and enriched by the geometrical hypothesis (Ehrlich's analogy of the pre-made *key-lock*), has turned out to be the winner. Both form the modern perspective offering the best explanation of *specificity* until now [30]. From the point of view of the origin of Ab diversity, few consider Pauling's instructionist hypothesis as viable nowadays.

The triumphs we describe here depend on multiple factors, but the prevailing methodology is perhaps the most powerful factor of triumph: the introduction of chemistry into biology favored Landsteiner; but then, the introduction of X-ray diffraction and the resulting visualization of crystallographic structures out of their natural context, strongly supported the isolationist perspective of the Ehrlich's key-lock metaphor. According to Marrack, the technological advances of the 20's, particularly in the diffraction of X-rays, radically altered the situation, since spatial atomic distribution and its effects were no longer a "graphic" hypothesis invented by Ehrlich for explaining the phenomena of specificity. Instead, they became a deduction from other sciences that was interiorized toward immunology, that is, spatial distribution could be seen now as a "genuine" explanation and not as an arbitrary illustration [26]. For this to happen, the antibodies had to be transformed into the crystalline substances in question, which permitted to have a system of structural characteristics grounded in the physiochemical practice; these were then interpreted as explicative variables [26]. It is important to point out that, although X-rays diffraction played a fundamental role in the establishment of the rigid metaphor of *specificity*, this being the experimental tool that materialized and confirmed the model of the *key-lock*, this model became established long before this methodology was invented. Diverse authors have proposed that the visual enchantment of Ehrlich's drawings was what "made this model real", especially this because the appearance of Ehrlich's images created an oscillation between biology and chemistry: the chemical iconography provided, so to speak, a skeleton onto which the flesh of biological representation was added [26]. Ehrlich's paintings are not "biological" in the sense of representing cellular metabolic processes, but in the sense of the pretension of the drawing about live images as a thematic resource[10]. Biology became a metaphor for Ehrlich and his contemporaries [59].

In fact, these drawings are considered as the direct ancestors of the geometrical forms used by the immunologist for representing Ag-Ab reactions, so much so that 1900 is denominated as the date in which immunological images are born [26]. After 1900 Ehrlich and his students made frequent and liberal use of diagrams, and those same diagrams or their variations were included in immunology textbooks and manuals[11] [26].

Ehrlich's drawings and how he used them are considered as being responsible for the rapid and extraordinary success of Ehrlich's "side-chain" theory, through according to Bordet, they are no more than "quite puerile graphic representations", science should construct its theories from "experimental facts" and not from graphic representations [26, 28]. The accusations of Bordet –"abuse", "trick" and "illusion"- suggest that Ehrlich used the drawings as an artifice, an invention for advancing toward a particular representation of the reaction between the antibody and the antigen[12] [59].

The image prevails over what at that time were accepted as specific tests; thus the symbols of the *key-lock* became the foundation of the theory of *specificity* and dominated immunochemistry (the new discipline that emerged from serology) for a long time [26]. According to Marrack, the notion of immunological *specificity* that had been "purely hypothetical" was materialized into specific atomic groups, that is, structural formulas became a method for representing chemical characteristics. The fact that the antigen joins an antibody like the key that fits into a lock is not at all an explanation, but simply a diagrammatical representation of the supposed facts [26].

All of this diagramming not only froze the biological process, establishing thereby the chemical-reductionist paradigm in the mental construction of the concept, and therefore of the *specificity* phenomenon, but it also caused alterations in its experimental approach: from the living thing to the test tube. The change from experiments with animals to experiments in the test tube, together with the adoption of the "stereochemical approach", quickly reached the iconic state. Ehrlich resorted not only to chemical tools and notions but also simultaneously to his images [26]. The physiological context was substituted more and more by in vitro studies on the *specificity* of antibodies and their corresponding serological reactions [29].

Finally, the association of the functional diversity of Abs with the genetic diversity of Igs was to strengthen even more the predestining theory of Ehrlich, to the exclusion of the instructionist one. Perhaps a mixture of chemical and spatial characteristics in the reactants in flexible interaction with the environment would offer broader approaches to immunological phenomenology (as we shall see later). Such a serene proposal is not yet welcome in the din of the disputes about immunological *specificity*, and even less so if the proposal implies wide margins of plasticity and co-determination in the antibody's molecule during the reaction with the antigen.[13] Evidently, the conceptions held by scientists in previous periods, which established the foundations of immunology, have been adjusted to fit in with the times in accordance with the "mental landscapes" of modern periods.[14] Sometimes these "metaphor transfusions between periods" take place without anyone noticing that this is happening. This may generate an interpretative transformation that assumes as facts things which might never have existed at all, i.e., ghosts.[15] One should not only look at but also learn from metaphors as being always locally applied, context-dependent, hence malleable units (like reality) of knowledge, partly responsible for the enormous dynamics of knowledge [5].

The *key-lock* metaphor possesses such intuitive charm that it has been investigated but little and has remained almost whole since its proposal at the end of the 19th century and the beginning of the 20th. It appears and is reflected on in a multitude of texts as something known and reliable, an unquestionable basis in debates, this in spite of the difficulties in its formal definitions, its measurement and the great amount of evidence existing throughout the 20th century in regard to its implicit plasticity in the face of the circumstantial [23, 24, 83]. The key-lock metaphor traverses our minds free of suspicions, unconcerned about its deficiencies, metaphoric tortuousness and stumbling-blocks, like the intriguing analogy of the "janitor's master key" (multispecific Ac) or the one about the "thieves picklocks" (an accommodating Ag for any Ac).[16] The key-lock metaphor has become generalized in other settings and other levels of biological organization, in which event there is supposed to be some sort underlying key and lock, i.e., a molecular recognition process, such, for example, is the case with certain drugs, hormones, endorphins, neurotransmitters, etc., whose effects are explained by postulating the existence of receptors that are not always sought out and demonstrated and are seldom formally studied as to their *specificity*who , and even less considering their molecular recognition in a living context.[17] The universality of this metaphor is indisputable; it can be found anywhere without difficulty, from children's puzzles, nuts and bolts, electronic connections and many more of our industrial artifacts, to the structure of nucleic acids and their consequent genetics[18] [60, 84]. It is, perhaps, the materialization of a physiology of knowing, understanding and thinking, historically determined[19] [1, 11]. This mental landscape may be said to imply a stiffened vision concerning the nature of Nature, in which images that are paired, disjunctive and antithetic always predominate [16, 17]: "... for every action, a reaction," "...for everything, an anti-thing," "...for a cavity, a protuberance."[20]

Once Ehrlich's metaphor and drawings had totally displaced complementary visions, in the era of molecular biology the chemical hypothesis of *specificity* lost ground to the geometrical one; later on the two were triumphantly united under the aegis of the *key-lock* metaphor. Perhaps both visions can fertilize and nourish the appearance of new mental maps in areas of investigation that are near or far from the Ag-Ab reaction. For example, it would not be entirely absurd in these times to propose that the structure of the water containing Ags and Abs in solution might be one o the main protagonists in the *specificity* of their union, and not only the chemical or geometrical nature of the reactants [77, 85-87]. The principal co-determiners of the water structure would be those molecules constituting a majority (e.g., ionic strength, albumin, lipoproteins, etc.); these would incline the Ag to react with the Ab, more than the molecular structure of the Ags and Abs themselves. The danger of simply accepting the *key-lock* metaphor as it is lies in its discouraging the consideration of other possibilities and inhibiting a deeper exploration regarding complex co-determination, as well as the biological consequences of a systemic and integrating vision of this process.

What is *specificity* in physical terms, what dimensions and measurements does it have, what changes it and how much, and is the change reversible? How operative is *specificity* in the natural functioning of the immune system outside the test tube? How are the requirements of the union for its instrumental identification related to the requirements for its expression in biological systems? How is the *specificity* of an Ab measured, considering the infinite number of possible Ags? Does specificity possess categories of amplitude and order when confronted with a set of ligands? How is it related with affinity? Does it have memory? Does a first reaction leave and imprint on the specificity of subsequent ones? Is *specificity* totally inflexible, or does it depend on environmental factors? Has its significance been changed through the emergence of other paradigms or mental landscapes, such as allostery? How does a set of receptor families evolve with a set of ligand families in an individual, in a species, in species generally?

7 The Plot of Mental Landscapes: Reconstructing Immunological Specificity

For Kuhn, the process generating a scientific revolution aids in the replacement of distinct and incompatible types of knowledge. This leads to the loss of valuable contributions in the course of the change in mental landscapes[21]. But not only the replacement of knowledge influences in its loss of significance; another factor contributing to the disjunctive extinction of mental landscapes in the search for unique truths is the Cartesian duality separating subject and object [88]. Cartesian duality creates the belief that concepts and explanations are mental entities independent of persons and historic moments, of experimental settings and of cognoscitive fields[22] [6, 7, 10, 89]. This has led us to use the metaphoric concepts conceived in previous times as though they were equally valid for reality as it is presently perceived. This has occasioned errors in the interpretations of terms, as knowledge is not product of a dual subject-object observation or perception; rather, it is strongly dependent on the instant-by-instant relationship of being and knowing[23] [8, 9].

In view of the problems in the conceptualization and construction of knowledge, the recovery of the biological sense of *specificity* will be possible only if it is built up within a systemic and contextual framework. In other words, we should ask about the biological-cognoscitive sense in the process of recognizing a multidimensional antigenic message, and how, by means of an enormously complex plot (determining parameters, some of which we will never be able to know), the immune system and the organism construct and give evolutionary and ontological sense to their specific response. To this end, it is proposed that the Ag-Ab reaction and its properties of *specificity* and extension occur and depend on at least: i) variables "intrinsic" to Ag and Ab molecules, ii) "extrinsic" variables associated with the environment and with the space-time in which the confrontation of the Ag with the Ab takes place, and iii) other contingent factors that are co-determined by what occurs between the Ag and Ab and by the "responses" of the environment and the organismic context to the Ag-Ab interaction.

Indeed, as we will see further on, innumerable studies at the molecular level, even in their empirical-reductionist phase, have repeatedly demonstrated that the principal functions and molecular qualities do not exist per se, but they arise and change as a product of a dialogic[24] on the molecule-molecule, molecule-cell, molecule-organism and/or molecule-environment levels. That is to say, the production of phenotypic characteristics is directed not only by the communicational-organization information of the genetic material, nor only by molecular-cellular processes associated with the genes (epigenetics); it is also the product of living dynamics; of the changes undergone by a phenotype with the passage of time (epiphenetics[25]). When conceiving a molecular level, therefore, we are speaking not only of individual substances loaded with material information (sequential, conformational, positional, etc.), but of a complex communicational-organizational network by means of which the different molecular subpopulations generate "senses" in differing instances (recognition, regulation, catalysis, transportation, contraction, etc.) of auto-eco-organization [15, 90]. The phenon (phenotype) arises from the interactions between the factors that originate it: its genes and its environment (the oikos). The recursive relations of genes-phenon and phenon-oikos demonstrate that what we perceive of the organism (phenotype) is an entity of great organizational and ontological importance. As we can see, the phenon (here we can consider the complex process of Ag-Ab interaction as a phenon of molecular recognition) is a part of the geno-phenomenic unit and is in turn related with the oikos (the totally of what the whole process means biologically). The phenon will be the tangible representation of both the auto and eco-poietic processes, since changes in its structure will be triggered by its relationship with both the genes and the oikos [14]. Thus, we see that the biological significance, in terms of reactivity patterns, of a certain Ab cannot be defined a priori; moreover, it is generated and regenerated as a significance that arises instant by instant [75].

The adaptation of phenotypic organizations to different stimuli[26], even to stimuli that are very similar, will be quite variable. In his studies on antibodies, Stuart Kauffman [91] has observed that, if the adaptive responses of the phenotype to different contextual circumstances are represented graphically, this will produce what he calls the **adaptive space** of a process (in this case, the space of possible reactivities of an antibody in response to diverse contexts of reaction). In this space one can clearly note how diverse stimuli can produce non-linear adaptive phenotypic responses; this demonstrates the organismic complexity underlying the process of immune recognition [91, 92].

Seen from this perspective, life in molecular recognition (and therefore in communication) goes through changes, interactions, competitions and cooperations that trigger and are triggered by macro-and-micro material processes as well as by energy fields [90, 93-95]. This broad phenomenological vision syntonizes well with the concepts that Bordet, Gruber and Landsteiner expounded at the beginning of immunology in regard to the colloidal nature of the molecular immune recognition process. In this space of complex co-determination observed as serological reactivity processes, molecular epiphenetics proposes that "intelligent" systems of interaction can be created through the molecular communicational-organizational process [96]. In such systems the molecular epiphenotypes as a whole process, utilize and generate organizational information, in other words, they compute [14, 97-100]. By means of such computations, the molecules can become aware[27] of their surroundings ("molecular cognition") and modify some of their attributes, such as their form and function [96, 101].

In this sense, "specific" discernment or recognition is a relational problem between a pair of molecules that recognize each other and the environment that determines them (structure, valency) [23, 102], in a given context and moment [83, 102-105], and that changes from moment to moment, that is, they are dependent on the spatial-temporal circumstances in which they originate [19, 24, 101]. From this dialogic, it becomes much easier to see how the immune system recognizes itself through its antibodies, and how it recognizes and communicates with the environment [19]. In other words, through specular images in its antibodies and the molecular and cellular regulation, the immune system creates and recreates its auto-eco-organized "selfhood."

8 The Intrinsic and Extrinsic Variables in the Process of Recognition: The Auto-Eco-Organization

In both theories, the determinist and the instructionist (in its isolationistic vision), the problem of *specificity* is conceived within the chemical and geometric complementarity of a pair of molecules (the ligand or Ag and the receptor or Ab). In the first, the *specificity* seems to depend on the intrinsic affinity of the reaction and is the measure of the quality of the adjustment between the antigen-binding site (paratope) and the antigenic determinant (epitope). The relation between affinity and *specificity* is not formally described, but in the most popular version the two are imagined as being in direct relationship, while in the stranger visions they are perceived as being inversely related [79, 106]. As for instructionism, specificity and affinity are constituted during the confrontation of the Ag with the Ab, both being dependent on the degree of precision in the joining of one molecule with the other [79]. Both visions rest on premises that deal with *specificity* as belonging to the same mental landscape as the isolationist key-lock, but they are assumed to be opposites because of differences in their degree of flexibility. As we have already seen, this metaphor ignores and rejects the enormous wealth of a vision rich in the contexts of living processes which was contrived at the end of the 19th century and the beginning of the 20th, when the molecular complexity and the colloidal forces participating in the co-construction of serological recognition were considered important [29, 30, 33, 55-57, 59]. In the one, there is rigid complementarity (key-lock) and the other, there is an adjustment in the form of both the key (Ag) and the lock (Ab) (instructionist) that takes place during the confrontation (Figs. 2 and 3).

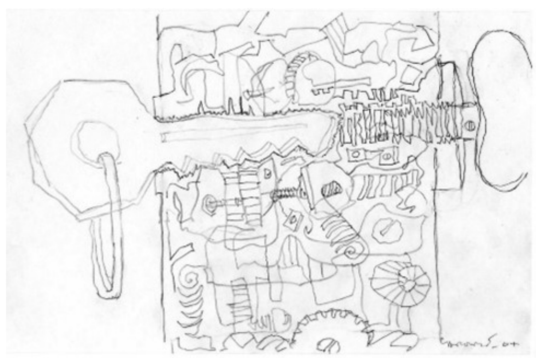

Figure 2: "Lock-and-key model".

Although the instructionist hypothesis turns out to be less restrictive, since it introduces a greater diversity in the repertoire of Ab's for the efficient recognition of Self and Non-Self, it is limited in that its biological effectiveness depends on the favorability of environmental conditions. In other words, within a network of structure-structure and structure-environment interactions, dynamics emerge that favor or inhibit interactions between the reactants, at the same time being sensitive to inopportune and/or deterministic perturbations [21, 83, 107].

Eugene Day adds another variable that participates in the *specificity* of the Ag-Ab reaction: the valency of the reactants, which he defines as the number of reaction sites on one single molecule of the Ag and Ab [79]. This consideration establishes a more realistic setting for the Ag-Ab reaction than the one built with crystalline structures of each molecule and with monovalent thermodynamic models. Multivalent interactions, in which two or more sites of a receptor make simultaneous contact with two or more sites of a ligand, may generate more perturbations in the extent and *specificity* of the reaction, as well as in the diversity of the products, than would be the case with a monovalent reaction [21, 83, 107]. In the middle of

Figure 3: "Instructionist Model": Masa, molde, intención y ambiente (Dough, mold, intention and environment)

the 20^{th} century, Pauling shakes simplistic models by encountering thermodynamic heterogeneity in every Ag-Ab reaction [78]. Since this occurs even with monovalent Ag's that are chemically and structurally ultra simple compared with the complex natural Ag's, it can only be concluded that, from an inflexible deterministic setting, the Ab's participating in one and the same reaction are not intrinsically equal [102, 108]. The importance of this finding was not completely understood in its time, but it indicates that Ab's are not mono-specific, not even the mono-clonal ones, but are able to react with an enormous spectrum of molecules, though having distinct affinity [109].

It is easy to imagine that *specificity* might also be a function of allostery, a property of complex proteins that would imply inter-and intra molecular interactions, during the occurrence of an Ag-Ab reaction. Such interactions can modify the intrinsic tendency toward the binding (positive cooperation) or unbinding (negative cooperation) of reactants [83, 102]. This sort of molecular contorsions can not only accomplish different degrees of adjustment in the surfaces and the results of a reaction, but can also organize the emergence of reactions that are absent in the original individualized molecules [110, 111]. This matter, previously disregarded, is nowadays considered trivially (as "conformational changes") in almost all phenomena studied under the general theory of receptors. Not everyone, however, regards the plastic and contextual phenomenon as trivial; indeed, various authors have postulated that it is not the number of molecular species but rather the quality of the material that makes adequate recognition possible, that is, its plasticity or evolutionary adaptability in the face of circumstantiality [23, 24, 83, 97, 112, 113]. For example, it has been proposed that molecules respond to the contextual stimuli of the communicational not through conformational changes that occur during the Ag-Ab interaction; in this, the quality of the binding is produced at least by the following factors: 1) conformational variations in the loops that constitute the Ab binding site (especially in L3 and H3, located toward the center of the binding site) [113], 2) changes in spatial positions or bearings (rigid body movements) of same [114], 3) rotations of side chains, 4) alternation in disposition between the variable light and heavy domains [115].

From this perspective, confronting the antigenic universe requires neither a great genetic "pool" nor processes of extremely rapid evolutionary variations, but rather plastic and adequate strategies that make it possible to recognize much with little [97, 98, 116]. The Ab repertoire is like a lexicon composed, not of words, but of sentences capable of responding to any idea expressed by the multitude of Ag's, be they Self or foreign, that the immune system may encounter [66]. Within this communication system, then, there is a need for grammatical rules to ensure a phonetically and semantically coherent framework for all sentences. Therefore, if the sequence or the proteic organization contains some information, it is not for creating or for producing a unique artifact as in the assembly of a "Lego" or the construction of a clock; rather, the content of information is like a guideline to permit interacting or communicating with an environment of forms, which Denton calls Platonic, pre-existent or pre-figured forms [112]. This suggests that the Ab, while possessing a certain amount of contextual plasticity, retains its organization to some degree, starting from a series pre-patterns of organization [112, 117]. For example, some crystallographic studies have shown that the structures of some proteins, when confronted with a diversity of spatial-temporal circumstances, can be incorporated in a series of fundamental forms or organizational pre-patterns [112]. A sample of this may be found in the crystallographic structures of some immunoglobulins, in which it has also become associated with some of their organization patterns having the capability of the antibody to recognize a certain category of antigens, thereby affecting the evolution of living beings [112]. Just as in the famous analogy of Aristotle, in which he considers that there is a pre-existent plan for the construction of a house that acts as a mold for its material components, bricks and stones, "so the order of things in the formative process is the reverse of its true and essential order. . . the bricks and stones precede the house chronologically. . . but logically the real essence of the form of the thing (the pre-existent plan of the house or the pre-existent form) comes first" [112]. What we have, then, are stored plastic forms that evolve under a grammatical or natural pre-form [112], forms which in turn are in a process of constant recognition or dialog with themselves and with the environment, in a constant exchange of "selfhood," in a constant process of auto-eco-organization [15, 58].

The pre-patterns are modified (as will be seen later) according to the communication of proteins with contextual factors that generate changes in their biological function and increase their adaptability [24, 97, 98, 102, 112, 118-120]. Due to the dynamic communicational-organizational process in which they are involved, molecules are thus able to modify their structure or organization pre-pattern according to the spatial-temporal situation in which they are immersed [112, 118, 119, 121, 122]. The foregoing is strengthened by evidence showing that, in a normal physiological situation, one protein can present several conformational states, one or more of which will constitute a majority, depending on contextual circumstances, as in the case of the infections protein "Prion" [121, 123, 124]. Some research done with X-ray diffraction in proteins indicates that some of their regions have segments of atoms in constant movement (intrinsic disorder), because they cannot be detected with this technique. This regions have been associated with the presence of certain conformational states, which may vary in accordance with the contextual changes in some proteins, that is, these proteins or one of their regions may be in a state of dynamic equilibrium (structural meta-equilibrium) among these conformational states under normal physiological conditions (Fig. 4) [118, 119]. In this way, proteins and molecules in general are shown to be in constant communication with the environment, by means of which they are able to process the organizational information generated in its and to dynamize their auto-eco-organization.

In this sense, the Auto-Eco relationship that co-determines the molecular recognition process, and therefore its *specificity*, can manifest itself in many ways. For example, molecular compression can also affect the specificity of different kinds of reactions, for according to the volume exclusion theory [125-127], in a compressed environment, the activity of each molecular species, whether diluted or concentrated, depends on the total composition of the medium. In other words, if the concentration of the molecular background increases, the magnitude of the effect of compression can become so great that the first site may lose its preference for the ligand it previously recognized and acquire preference for another [125-127]. But not only the molecular density of the environment is involved in *specificity* and cooperation; other factors inherent in the Ag-Ab complex and in the environment contribute to modify the energy of molecular interaction. The *specificity* and the extent of the reaction may be altered not only in accordance with its concentration but also with the size of the surrounding molecules, for instance, the tiny molecules of plasma (e.g., small proteins, peptides, carbohydrates, ions, +Page 76. Paragraph 2, raw 7. As to instructionism: As co-participate in the Ag-Ab reaction by establishing fleeting but frequent equilibriums with the more active groups outside the Ag and Ab molecules. These interactions also occur with water, being able to

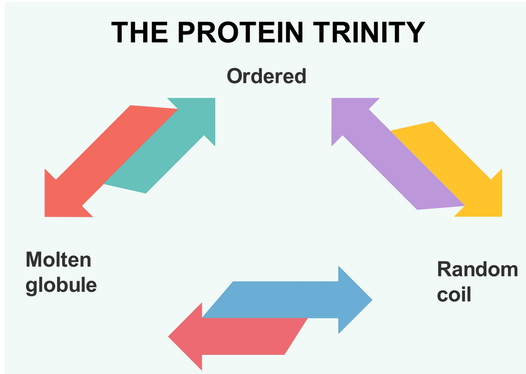

Figure 4: An alternative hypothesis for protein structure / function. As shown, The Protein Trinity suggests that the *native* protein structure includes not only the ordered state, but also random coils and molten globules. Further, this hypothesis suggests that function can be carried out, not only by the native state, but *by any of the three states or their transitions* (figure from Dunker [118]).

perturb the reaction by altering its specificity and extent [128].

The temperature, pH, ionic strength and concentration of salts alter the Ag-Ab reaction, changing the distribution of charges and upsetting the balance in the solution of the molecules involved; this could also change their conformation [24]. Calcium and other ions increase or decrease the magnitude of the precipitation of the Ag-Ab complex by several degrees, since they can stabilize this complex through the quelation of polypeptide chains or by favoring small but effective conformational changes [24]. In addition, crystallographic studies have revealed that water plays a central role in the Ag-Ab interaction, because its molecules can improve the adjustment of complementarity in and around the Ag and Ab interphase [129, 130].

In biology, water is generally assigned a merely passive role as "universal solvent," that is, it is assumed to be the "substratum" where life's chemical reactions take place. Nevertheless, things are not that simple; to begin with, different kinds of water exist in a cell: bound water, hydrating water, vicinal water and free water. Even if we consider as correct the estimate that approximately 95% of cellular water is not bound, this "free" water is not a fluid (not viscous) medium that fills the spaces left free of cellular structures. On the contrary, it seems that water contributes decisively to the structural organization of the molecules of living cells [77, 85]. Detailed studies show that water is able to form orderly transitory aggregates which remain joined by means of cooperative intermolecular bonds. These basic units interact actively with macromolecules, thereby contributing to their own coupling and organization [23, 77, 85]. There is a diversity of evidence to indicate that the organization of water predetermines the adequate geometric dimensions for the functioning of the macromolecules in the living cell, examples of this are the dimensions of biological membranes, the domains of proteins and of nucleic acids, which responds to this geometric requirements [81]. There is also evidence that water actively contributes to the transitory "anchoring" of "soluble" proteins to the cytoskeleton network, thus facilitating the appearance of the metabolic channeling phenomenon, which enters the scope of vectorial biochemistry [85].

Besides the direct effect of water in the interaction, and apart from space, time and causality, "memory" associated with the water should be added to all biological phenomena [34]. Not only is organizational information generated, received, processed and transmitted during molecular communication; there is evidence that the molecular epiphenotype is able to store this information [120, 131, 132]. For instance, studies done on some proteins, such as lysozyme, indicate that when this molecule is placed in a solution having a known pH, it presents a certain number of conformations per unit of time [133]. When the pH of the solution is modified, the number of conformations varies; but when the pH is adjusted to its previous level, this number does not return to its original value but to a lesser one [133]. From the foregoing, it is concluded that lysozyme and other components of the oxidating mixture exhibit a memory of pH from their previous solutions [133-136]. It is proposed that this happens because the enzymes are able to store and to use the information generated as a result of the movement of their quantum particles in the communicational-organizational process of their previous solutions, a characteristic called molecular memory [132, 137-147].

A well-known example of molecular memory associated with the organization processes of quantum particles and with subtle fields of energy is the memory of water [105, 132, 139, 142, 148]. This memory of water has been observed in studies which show that the activity of some molecules, like those of medicines and antibodies (active principles), is retained by the molecule of water [86, 87, 139, 142]. Such a memory allows molecules to communicate with one another by exchanging information without need of physical contact. Consequently, it is not only the molecules and atoms present that perturb *specificity*, but also the electromagnetic vibrations or spectra that flow through and are preserved in the water [77]. This is supposed to happen because water favors the exchange of electrons with the active principle in solution, sometimes through the generation of hydrogen bonds that create certain vibration states in the water molecules [105, 139, 142, 148]. On account of these vibrational states, it is proposed that water is able to store, to transmit and consequently to mimic the biological activity of other molecules [139, 142].

It has been observed that molecular actualization, communication and computation through the quantum biofield are aided and potentiated by water, thanks to its many intrinsic attributes [105, 149-151]. For example, the structure and organizational properties of water allow this molecule to transmit, through its network of hydrogen bonds, electrons "belonging" to the macromolecules dissolved in it. Because of this, water becomes a participative environment in regard to the electrical changes in other biomolecules, influencing their conformation and facilitating electronic tunneling processes in the organism as a whole [105, 149-151].

Such evidence outlines the possibility that, at the molecular level, the communicational-organizational process may also take place by non-material media through subtle fields of energy [132, 137-147]. There is a diversity of research that reinforces the foregoing by showing that subtle biofields of information, specifically the electro-magnetic field (EM), can modify the intrinsic attributes of various biomolecules [132, 146]. In a "normal" physiological environment, this occurs because some biomolecules, particularly proteins, are able to produce electrical charges; these can generate their own EM field, which may interact with an external EM field [122, 137, 147, 150, 152-154]. Thus it is proposed that some molecules, especially proteins, are able to process, transmit and potentiate the organizational information of subtle fields of energy (in this case, the EM field), with non-linear effects on their form and function [122, 132, 137, 147, 150, 152-154].

The quantum field, another biofield that participates in the molecular organization of biological systems, directs the processes of the atomic sub-particles composing the micro-and meso-scopic states of biological systems [122, 140, 141, 145, 147, 150, 153, 155-157]. This organizational field manifests its action principally in the states of synchronic and harmonic movement of atomic sub-particles (quantum coherence), which have been observed to produce repercussions, from the molecular up to the organismic levels, in the process of communication-organization between living beings and their environment [122, 140, 141, 145, 147, 150, 153, 155-157]. This occurs because the movement of electrons in the quantum field creates a displacement of the protons and neutrons (nuclei) of a molecule; these express themselves as structural changes with functional repercussions, which are called Electron-Conformational Interactions (ECI) [122, 138, 150, 154].

The coherent behavior resulting from the communication and isolation of biomolecular systems with regard to biofields can be perceived in the preferential conformation of a molecule, a state of quantum coherence known as "conformon" [138, 150, 156, 158]. Some research done on aspartate-aminotransferase and some other enzymatic and cellular complexes reinforce this notion, showing that their interaction with some biological targets creates coherent electronic movements which generate ECI's at their active site, thereby producing a "new" conformation or conformon [122, 138, 158-160]. The quantum coherence expressed in the conformons has been observed to modify itself according to space-time circumstances and to influence the interaction among molecules, even before establishing contact with them [138, 156, 158]. Therefore, the communication among molecules and, consequently among cells, tissues, organisms, etc., through the aforesaid state of quantum coherence, will modify their relations or their *specificity* with regard to the other organismic components [158]. Conformons are states of quantum coherence associated with a certain conformation within the same molecule; however, there is evidence that this coherence can be transmitted and co-generated collectively among different molecules, cells or organisms [141, 157]. In the quantum field, this can be observed in the production of solitons, by which information and energy can be transmitted through this biofiled [158]. The soliton is a single gigantic wave generated by the collective coherent movement of quantum particles in one or several molecules [150, 151, 161]. In this state of quantum coherence, the kinetic energy of all the particles is distributed equally throughout the wave, as in a superconductor; this generates the Frohlich effect, thus nullifying the energy lost [150, 151, 161]. In this context, we can observe that the complexity of the autopoietic process in which the co-determination and evolution of the genos, fenon and oikos occur, it cannot be explained since a lineal mechanicist logic only. That is, during the process of molecular recognition and particularly during the Ag-Ab reaction, profuse events occur within the organism (and even in the test tube). In other words, we are in the presence of a scheme that is much more complex than what we can see on an X-ray diffraction plate, where the photograph shows only one instant of the reaction process, besides eliminating all background or context: the vital field [141, 157].

Of course, the chemists, physicists and immunologists of the golden age of the Ag-Ab reaction, around 1900-1970, did not ignore the possible participation of the complex scheme of the aforementioned variables in the reaction [137]. At present, it appears evident that they grossly underestimated the magnitude of their joint effects. This may be the time to set up a more complete and flexible theoretical framework to incorporate the multimodal complexity of *specificity* in order to better understand the key reaction of immunology at the molecular level.[28]

Greenspan and Cooper [104] propose another meaning for *specificity*, which involves the biological effect. This meaning is based on observations that the degree of affinity of the Ab for the Ag (and vice versa) is not necessarily related directly to the magnitude of the biological effect, that is, binding can take place without a biological effect. Therefore, immuno-biological *specificity* may diverge from immuno-chemical *specificity*. This effect has been defined as a product of the "localization, dose and time of exposure." In other words, it is not possible to generate a second signal (which is the one that produces a biological effect) if the binding of the immunological reactants does not take place in lymphoid tissue, or in the concentration or the time necessary to trigger the second signal [162].

In short, *specificity* does not exist by itself; it is created at the moment when a receptor unites with one ligand but not with others. This refers not only to the Ag-Ab pair, for *specificity* is a product of the environment, in a certain space and time and connected with some discernible biological event. As Van Regenmortel already proposed in 1989 [23]; it is a relational phenomenon.

There shall never be a door. You are inside
and the fortress holds the universe.
There is no obverse or reverse
no external wall or secret kernel.
Do not expect the rigor of your journey
which divides itself into another
will have an end. Your destiny is like iron
like your judge. Do not wait for the bull
that is a man to charge, whose strange and varied
form horrifies the thicket intertwined with stone.
It does not exist. Expect nothing. Not even
The beast in the dark twilight
Jorge Luis Borges (Translation: Adriana Menassé) [163].

9 Conclusions

9.1 Toward New Mental Landscapes in an Integrative Epistemology

In modern times, the quest for certainty has formed an essential part of the edification of knowledge [2]. Cartesianism has yearned to find a mechanical universe and an objective, aseptic rational mind that would be mutually complementary. The Baconian image of a scientist distressing nature to make her reveal her secrets closes the pincer of dualism [7]. This promise would make it possible to describe reality with even greater accuracy. But what enables science, or rather the human being, to know? The modern synthesis of learning and the recent epistemological crises, e.g., in physics (the quantum paradigm, the sciences of chaos) or in biology (the epigenetic field, ecological complexity), have impelled us to pose the underferable question of "knowing knowledge" [8]. Objectivity and mechanism start to vanish before our eyes in the face of the evidence from the cognitive sciences, that is, we begin to realize that Cartesian dualism and scientific objectivity operating alone and extraneous to a dialog among branches of knowledge are chimeras that paralyze knowledge. The universe is an immense and unfathomable complexity that requires systemic and contextual focusing. Absolute certainties, therefore, end up imprisoning us in mental paralysis, in which we need to empty nature of her complex interactions and her systemic character in order to fill her with restrictions, thus adjusting her to a model of clockwork that promises predictability and certainty. We call this the secularization of knowledge and, by extension, of nature [164].

In approaching the immune system, this reductionist process meant ensuring that this system would act through specific molecular agents: being the antibodies the mechanisms of discrimination. In consequence, the reductionist-mechanist vision conceptualizes molecular agents containing "*specificity*" as something autonomous and unvarying. But this could only be fabricated when the biological context of the reaction was emptied of living, systemic and energetic contents, i.e., of its structural co-determination. Thus isolating the process of molecular recognition from its environment (which gives it its meaning) allows the construction of a sphere of conceptualization and experimentation that has little relevance in the immune system and in non-aseptic environments in general. By building the mechanistic secularized concepts and from this experiment, the possibility of "measuring and seeing" a mechanical and predictable object is ratified for conditions that are empty of meaning. This confusion is related to the old philosophical dispute regarding substance and process, i.e., the reductionist vision has insisted on concerning reality as "substance" [7, 90], with its qualities residing exclusively in the material structure, thereby denying its transitory and dynamic scope (the relational field), a scope which likewise determines the properties of the system. The receptor does not recognize in a vacuum; instead, multiple determinants (such as the cellular membrane, the effect of epitope density, the concentration of receptors, the bundle of accessory molecules for the receptor, a complex network of supracellular interactions, biofields, etc.) give the recognition its meaning. As we now know, affinity constants or very high concentrations of antigens inhibit the unleashing of some immunological responses. No recognition, not even that of an engineering antibody, obeys deterministic laws; therefore, the certainty and mechanism of clockwork proposed by a static and isolated vision of molecular recognition begins to collapse. The system and its relevant fundamental properties disappear when they are dissected and emptied of their operational integrity. For this reason, movement and relationship in dialectic synthesis are central elements of the system, just as Berthalanffy and Goethe visualized [14, 15, 90].

If it be possible to recover a contextual and biological sense in our notions of *specificity* and immunological complementarity, thus generating polyphonic and non-exclusive descriptions of local truths, the setting would seem to point toward a systemic and contextual framework, that is, we should ask about the biological-cognoscitive meaning of the process of recognizing a multidimensional antigenic message. In addition, we should ask ourselves how the immune system and the organism construct and give evolutionary and ontological meaning to their response by means of an enormously complex scheme (some of whose determining parameters we can never know or even imagine). It is the total process that synthesizes and gives semantic value to the Ag-Ab interaction, making it possible to provide an appropriate biological response, "appropriate" being a transitory and contextual quality. Therefore, with the intention of reducing our knowing as scrupulously as possible, we could say that we should at least ask ourselves: What is the *specificity* of an Ag-Ab reaction in a given serological and organismic context and or a given history and environment?

9.2 The Context and the Immunological System

This perspective visualizes *specificity* as a dynamic and contextual of the biological processes of discernment in a complex relational scope [23, 24]. It differs from the established perspective in which *specificity* is a static and absolute property of things. We have suggested herein that the *specificity* only becomes meaningful when placed within a certain space and time. Consequently, the processes connected with *specificity* will also be relational and emergent phenomena.

Since immunological *specificity* has historically been placed in the center of immunological functioning, the recent transformations and enrichments in the mental landscape of this concept will have important consequences on the understanding of the immunological system. At present, the prevailing model regarding the immunological system is based on Burnet's theory of clonal selection [33, 165]. Essentially, this vision implies that the immune system functions on the basis of the dynamics of Darwinian clonal selection of lymphocytes, in which the clones with their respective receptors having the combination of greatest specificity and affinity for the antigen are selected and stimulated. From this basis of the fundamental dynamics of adaptive selection, the army of clones in "combat" will, in combination with the complementary molecular, cellular and tissular machinery of the immune system, elaborate an immune response that is destructive to the pathogenic agent. Consequently, it logically, follows that the fundamental processes of the immune system (such as regulation, tolerance, memory, etc.) will depend on the control exercised by the system itself over specific clones and their receptors. The selection model is complemented by the affirmation that immunological system functions by discriminating between the "Self" (defined early in development) and the "Non-Self" (all that comes later), tolerating the "Self" and attacking the "Non-Self" [63, 64]. However, enormous blank spaces still exist in our present understanding of the global processes occurring in the immunological system, this notwithstanding the fatuous and astonishing availability of thousands of data and descriptions about the immunological system's hundreds of molecules, cellular sub-populations, tissular arrangements, etc. Many questions remain to be satisfactorily explained, e.g.,: How does the organism pass through its stages of development (puberty, metamorphosis, pregnancy and aging) without new and modified tissues being attacked as they appear? Why are we unable to produce immune reactions against foreign inert proteins unless we simultaneously add other substances, called "adjuvants"? Why can the immune system tolerate a viral antigen when this expresses itself as an auto-antigen in a transgenic mouse, whereas this tolerance subsequently disappears when the mouse is infected with the virus? Under a militaristic model repressive of clones having "undesirable" reactivity, it is impossible to explain these phenomena which denote an essentially cognitive system with great plasticity. These and numerous other questions and observations tell us that the context in which an infection occurs is just as important as the infectious agent itself.

The work done by Jerne and his collaborators concerning the hypothesis of the immunological network during the past 30 years shows that the diverse fundamental properties of the immune system (such as memory and tolerance) are supraclonal phenomena that are independent of the "unvarying" molecular details of specific receptors [69, 166, 167]. Thus, for instance, immunological memory is not a consequence of the exclusive Ag-Ab interaction; even less does it reside in just a few cells [166]. Autoimmunity is not a defect of the Ab's secreted by B cells or by the presence of autoreactive cells, since these populations exist naturally in healthy organisms [167, 168]. These auto-antibodies exist in the organism independently of the entrance of a foreign "bug" into the system. The same can be said about infections: they are not to be regarded as a battle with victor and vanquished. The dichotomy between external and internal (between "Self" and "Non-Self") is artificial; there is considerable evidence to indicate that the immune system operates for a continuous survival that responds to both the internal and the external to ensure the functional harmony of the body [63, 71]. The discrimination between the "Self" and the foreign is a systemic property relative to supraclonality, that is, in the most general sense, immune Selfhood was equated with normality – in fact, with ideality [169, 170]. This already heralds a postmodern orientation in that a static "norm" is replaced by an endless quest for idealization. The organism not only ceaselessly strives for its self-aggrandizement vis-á-vis others, but engages in a constant surveillance to achieve inner perfection [33].

Since Burnet formally introduced the "Self" metaphor in 1949, a great amount of evidence has accumulated to indicate that the immune system operates for the continuous survival of both the internal and the external, thus ensuring the functional harmony of the body [33, 63, 71]. Immune is now conceived by some as a derivative, being at present the product of a positive process of self-identification. With this revised notion of immune identity, a new dimension of complexity has been introduced [33]. From this perspective, the discrimination between the intrinsic and the extrinsic is a systemic property relative to the supra-clonal one, in which the immune system defines Self and Non-Self in a contextual dynamic or Selfhood [33, 167]. All of the foregoing emphasizes the need to abandon rigid and deterministic mental maps and to redirect ourselves toward others that include dynamic and complex cognoscitive properties. "Complexity is not a solution word, it is a problem word" [2].

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Footnotes

1. Known as a rhetoric device within the literary discourse, a metaphor serves to re-describe a phenomenon, as yet problematic or unknown, in an eloquent and familiar way [5]. A metaphor thus contributes to enlighten the recipient with respect to the phenomenon described, and also sheds new light on itself. But metaphors may also be deceiving when transported from their original use and context to the new one [5].

2. The relation between the theories can be based on a dialogue involving diverse approaches, instead of a direct confrontation, that is to say, in the possibility of taking advantage of its co-present and diverse hypotheses. It allows us to leave the identity of the different points of view unalterable, and at the same time to activate fantasies and images. The imagination, setting in the boundary between the somatic and the psychic, allows us to transform impulses into something representable to restore the symbolic capacity, which can be directed to the elaboration of outside experiences [171].

   From this perspective, the imagination does not serve to deny reality and to construct a world that allows us to satisfy omnipotent and hallucinatory desires and affective impulses, but rather to explore possibilities [171].

3. Contact with reality does not induce answers, but instead provokes questions, "the hypothesis is inspired by the necessity to pose questions - but not necessarily to respond" [172]. Metaphors can be the ghosts of ideas that hope to be born. Although by themselves, metaphors do not describe "dead objects" or meanings already attributed, but growing states, not yet well determined and expressed [171].

4. Paradigms have come and gone throughout history, causing the course of knowledge to separate scientists into two groups: one, a speculative group that tries to unify nature's diversity; the other, a more practical and empirical one that tries to differentiate nature in order to accentuate her diversity [173]. In this respect, Lewin [174] and Wilber [175] declare that the debate goes back to the beginnings of Aristotelian science, when objects were divided into well-defined classes; its counterpart is to be found in Galileo's ideas regarding the unification of the physical world. For Kant [173], this unity exists in the human mind, since nature is diverse in itself, that is, since knowledge is scientific only in proportion to the rationality contained in it, the multiplicity of nature becomes scientific upon being converted into a continuous species in the human mind [30]. In his book, "Principles of Mechanics," Hertz [176] likewise notes that: "It is true that we cannot demand simplicity from nature a priori; less still can we judge exactly what is implied by 'simple." Where we can convince that if these images are properly adjusted to things, the relationships among the things should be represented in a simple form. But if the real relationships among things can be represented only in complicated form. . . we decide that these images are not well adapted to the things. Therefore, our simplifying mental restrictions cannot be applied to nature, but only to the images we fabricate; our reluctance to accept complicated declarations as fundamental laws only expresses the conviction that the content of declarations is not correct and understandable unless it can be expressed in a simple and more convincing manner than the fundamental concepts [176].

5. It would be well to reflect on the following: If it is the mind that fundamentally simplifies or complicates nature and this vision does not mirror reality, its observation and conceptualization will depend on the focus used by the observing subject. In other words, the phenomenon of knowing cannot be taken as if it were a heap of "facts" or objects external to the brain and perceived by one. Experiencing anything is valid only at the moment when the human structure makes it possible. "All knowledge depends on the structure of the one who knows." [8]. Therefore, the act of knowing is inseparable from what is perceived and from the one perceiving, which leads us to recognize our participation in the construction of reality and of knowledge [10].

6. The concept "auto-eco" was first proposed by Edgar Morin [14-16]; it relates the origin of genesis to a recursive loop (feedback cycle) co-generated through internal "auto" (organism) and external "eco" (environment) dynamics, as well as to the complex interaction between these. Actually, one cannot exist without the other, so it is impossible to reduce one to the other or trace the precise origin of either of them (hence their "dialogical" dimension); they co-generate each other mutually and instantaneously [14-16]. The organization that generates the organism that generates the organization -this organization being both internal and external- the environment that generates the organism that generates the environment.

7. "This circularity, this linking of action with experience, this inseparability between a particular way of being and how the world appears to us, tells us that every act of knowing puts a worlds in one's hand: the being and doing of an autopoietic unit." [8]. We call this vision an ethic of knowing, that is, a dialoguing polyphony of complementary knowledge, a space in which we find possible universes rather than absolute and exclusive truths.

   In accordance with this perspective, we believe it necessary to change the term "paradigm" to that of "mental landscape" [177], since observable reality will be the product of the perceptions and pre-conceptions generating all that makes up the observer and the object observed (physical, mental and spiritual). In this sense, as regards the generation and evolution of science, the act of knowing could consist in abandoning the opposition plane and changing the nature of the question; this would result in a more comprehensive context.

8. In consequence, a scientific revolution would imply a synthesis and cohabitation between new and old knowledge, in contraposition to the stand taken by orthodox science, which has assumed as its duty, in defense of new knowledge and "truths," to destroy and negate the ideas that ruled before the paradigm was changed, causing other knowledge of a different and incompatible kind to be replaced [27].

   The adoption of an ethics of knowing by the scientific community would impede the loss of proposals already achieved during the change toward the enrichment of mental landscapes. An illustrative example is Lavoisier's chemical theory, which was disseminated throughout the 19th century and which prevented chemists from posing the question of why metals were similar, a question which had already been posed and answered by phlogistic chemistry. The transition to the mental landscape of Lavoisier meant not only the loss of a question but also of the solution that had already been achieved, it being as partial as the other explanations with which it cohabits [27].

9. Especially because of Bohr's theory of complementarity, which was to produce the first doubt about the Newtonian-mechanist model. In modern relativistic physics, matter bears more resemblance to a sequence of events than to a collection of substances. This change demands a new conceptualization of matter and of reality in general, not as a fixed substance or as an accumulation of static particles, but as processes, as events that take place in time, made up of electromagnetic and gravitational fields in intimate interaction and of a complexity of nuclear forces of energy [3].

10. Universal terms must be treated as "symbols" that simply allude to a certain form of matter. It is not possible to speak directly of an object, but only to approach it in various indirect ways [10, 171].

11. Contributing to its popularity was a set of eight drawings, which have since been often reproduced. One of those drawings is still the logo of the journal Immunobiology, created in 1909 by Ehrlich [26].

12. The images are not only representations of meanings; they enclose, above all, the significance conferred them by the thinker, they are in contact with the "pathos" of knowledge. They describe the direction of the research rather than its result [171].

    The imagination, being situated on the boundary between the somatic and the psychic, makes it possible to transform pulsations into something representable by establishing the symbolic capacity, which leads to the elaboration of outside experiences. In addition, the imagination is situated precisely at the limits between the internal world and external reality. It is not utilized, as is fantasy, to satisfy affective desires and impulses in an omnipotent and hallucinatory manner, but to edify and hypothesis of the interpretation of the world and a project of action upon reality. Its purpose is not to renounce really or to construct a world "as if," but to explore possibilities [171].

    ... "it would not have been impossible to obtain some sort of physics and chemistry without postulating the existence of atoms, but it would have been much more complicated and science would have been less attractive" [178].

13. Albeit not all scientists have been blind to the changes proposed by a new vision. Here it is note-worthy to mention the comment made by Darwin [179] upon finishing his book "The Origin of Species": "Although I am fully convinced of the truth of the views given in this volume under the form of an abstract, I by no means expect to convince experienced naturalists whose minds are stocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine. It is so easy to hide our ignorance under such expressions as the 'plan of creation,' 'unity of design,' and to think that we give an explanation when we only restate a fact. Anyone whose disposition leads him to attach more weight to unexplained difficulties than to the explanation of a certain number of facts will certainly reject my theory. A few naturalists, endowed with much

flexibility of mind, and who have already begun to doubt on the immutability of species, may be influenced by this volume; but I look with confidence to the future, to young and rising naturalists, who will be able to view both sides of the question with impartiality" [179].

14. Knowledge varies among individuals, groups, discourses, or subsystems and changes over time. This property, in which different factors stabilizing the variance of knowledge, allows social interaction to occur. From this perspective, the dynamics of knowledge can be observed as a process of continuities and discontinuities, specializations and integrations, or locally specific variances and stabilizations. The processing of metaphors gradually produces heterogeneous sets of meanings across various types of discourses for a given period of time. For this reason, it is necessary to treat universal terms as "symbols" that simply allude to a certain matter. It is not possible to speak directly of the object, but only to approach it by several indirect routes [5].

15. Besides this, the scientists of previous periods are represented implicitly as though they had been working on the same set of fixed problems and experimental models, and in accordance with the same set of unmistakable canons pertaining to the most recent revolution. Newton wrote that Galileo had discovered that the constant force of gravity produces a moment proportional to the square of the time. Actually, the kinematic theorem of Galileo takes shape when it is inserted into the matrix of Newton's own dynamic concepts; but Galileo said nothing of the kind. Boyle's definition of an element was nothing but the paraphrasing of a traditional chemical concept. Boyle offered it only as an argument to show that what we call a chemical element does not exist; therefore, the version in textbooks alluding to Boyle's contribution is absolutely erroneous [27].

    Due precisely to their epistemological profoundness, metaphors are indeed tricky figures of speech that are valued very differently. While they are highly welcome in poetry and rhetoric and a regular occurrence in everyday language, they are mostly rejected in the sciences. As foremost exemplars of the improper use of language, they deeply threaten the ideal of objective knowledge couched in literal terms. But if we study the functioning of metaphors in various domains of thought and discourse, we can see that metaphors are unconsciously and automatically objects, frequently used as basic cognitive concepts that guide the production of discourses and therefore, the dynamics of knowledge [5].

16. The assumption is that the concept and its movable discourses interact with each other in just the way a metaphor in a poem does, that is, eventually both metaphor and poem acquire new shades of meaning [5]. Considering all these properties of metaphors, we could make an effort to consider the "movement" of the phenomenon, and its continuous transformation. This does not imply returning the imagination to the process from which it had been excluded; on the contrary, it entails the necessity of overcoming the dichotomy reason-imagination (or reason-passion), which reduces the multi-dimensional vision of the mind to a bi-dimensional model [171].

17. Metaphor reflection challenges the long-standing idea that 'literal' representations of the world are basic and figurative or that metaphorical representations are distortions, and it introduces the notion that the same metaphors can be processed very specifically by different discourses, like one antibody could have different biochemical "activities" in different contexts. For this reason, when metaphors are constructs foreign to a discourse, they lose their metaphorical status: they are 'de-metaphorized' [5].

    In fact, de-metaphorization (without a contextual and organic thinking) causes a misuse and/or abuse of metaphors, which also provokes their elevation to the level of scientific truths: they suffer a process of 'scientification' [5].

18. The single most important feature of a term or phrase used as a metaphor is that it is 'nomadic', that is, taken up by and interacting with various discourses over time, thereby showing their malleability both actively and passively. The vague nature of a metaphor allows it to float freely between contexts

of use. Metaphors are neither good nor bad, they are omnipresent elements in any type of discourse, therefore, ideal targets of discourse analysis [5].

All of this encompasses the process by which metaphors become like 'viruses of the mind', multiply all of-a-sudden, diffuse into many different contexts of meaning, and eventually, after having caused major changes of perception and interpretation, fade away. Put non-metaphorically, the concept can be said to have lost its status as a metaphor, that is, as a versatile unit of knowledge communicating with various discourses, thereby transferring and transforming meaning(s) [5].

19. In other words, knowledge is locally specific and context-dependent. Our conception allows us to follow the career of single terms or phrases, as well as the change they induce in the movable discourses. Knowledge, in this sense, is a cultural project produced at a multiplicity of discursive sites, interspersed with practices and technologies of different kinds. Its transferability and its linking function contribute to the emergence of its global significance, local differences notwithstanding [5].

20. It is essential to dislodge those forms and obscure forces that are behind the custom of interconnecting the discourses of men; they must be cast from the shadows in which they reign" [180]. And it is that "...as a species, we are still afraid of our own opinions" [34]. Or, as Bateson puts it, "we have epistemological panic" [181].

"Instead of setting a basis for what already exists, instead of tranquilizing ourselves on account of this turn of events and this final confirmation, instead of completing this happy circle announcing the end, after a thousand sly acts and as many more nights, that everything has been saved, we are obliged to advance beyond familiar landscapes, far from the guarantees to which we are accustomed, over terrain that has not yet been surveyed and toward an end that is not easy to foresee" [182].

Because of this fear of uncertainty, we are tempted to name (metaphor) and to group things, which appears to be inoffensive. However, it makes us tend to forget that "the map is not the territory" [183] and that "the best map of the territory is the territory itself" [163].

"We must leave to the Judge experimenter and leave its place to a deciphering naturalist, to an investigator whom the narration like a pale reflection of its activity of laboratory considers not only, but the best instrument to be reconciled with the objects of its investigation" [184].

We want peace at the verbal level, i.e., at the level of thought.... But the word "peace" is not peace

– - Jiddu Krishnamurti [9]

Words behave like capricious and autonomous beings

- Octavio Paz

21. Although there are many circumstances that conspire to extinguish scientific discoveries, a special inhibition evidently exists toward that knowledge which causes malaise toward our inviolable cultural norms. We cling to that knowledge which respects the perceptual agreements of the prevailing current [34]. In every society the production of discourses has been controlled, selected and redistributed through proceedings of exclusion–exclusion that not only prohibits but also separates and rejects in response to the exercise of a power [185]. From all the foregoing, we propose that a new theory need not necessarily enter into conflict with any of its predecessors. "They are neither less scientific not more the product of human idiosyncrasy than the present ones. If antiquated beliefs should be called myths, then these can be produced through the same kinds of methods and supported by the same kinds of reasoning that lead to scientific knowledge at present" [27].

"In any case, those settlements - be they the ones that we admit or those that are contemporary with the discourses under study are themselves always reflexive categories, classification principles, normative rules, institutionalized types: they are in turn made up of discourses that deserve to be analyzed along with the others with which they undoubtedly have complex relationships but which are not intrinsic, autochthonous and universally recognizable characters" [180].

"According to Bono, scientific graphical models, rather than being a result of 'inexplicable gestalt-like change as with Kuhn and Foucault' [186], can be rooted in the destabilizing tendencies inherent in any scientific language. From this perspective, scientific terms, concepts, and discourses are related as 'hybrid'; even the most coherent of them will prove inherently unstable, and, when 'exacerbated by the interference of social, cultural, or ideological factors, such tendencies' may prove disruptive and produce change [186]. Thus, Bono deems negotiation rather than revolution to be a more fitting model of scientific change – given the complexity of metaphoric exchange underlying it" [5].

22. Therefore the act of knowing is not the product of a dual subject-object observation but is strongly dependent on the being-and-knowing relationships. Knowledge is an alert perception, from moment to moment in regard to each thought as it arises in the relationship, i.e., "the very perception of what we are, just as we are, at the moment we act in the relationship, brings freedom with it in regard to 'what is'" [9]. Or, to put it in other words, "it is essential to renounce all those topics whose function it is to guarantee the infinite continuity of the discourse and the renewal of its secret presence, to be willing to receive each moment of the discourse as it happens to irrupt... The discourse is not to be returned to the faraway presence of its origin; it should be dealt with in the scope of its urgency." [182]. Knowledge is not accumulative, it does not evolve, it simple is at the moment of being conceived within a mental landscape and put into the form of discourse.

    Thus BEING and KNOWING are relational and perturbable entities in constant construction. Such construction is a result of balancing cognoscitive processes or reorganizations (disorganizations that become organized in another way) [89] and the interweaving of realities and mental landscapes during an historical event.

23. "Names, words or ideas give us the false sensation of knowing an object, since an idea that seemed strange or unacceptable can be reduced to a more familiar or acceptable significance" [10]. However, each word does not indicate anything external to ourselves; it is but an element in the flow of our coordinations of actions and emotions, that is, the significance of words does not be in the words themselves but in the flow of the behavioral coordinations in which they participate [8].

    And I tell the rock:
    okay rock, now you can soften,
    wake up, stretch out,
    cross the limits of your kingdom
    be yourself, be mine,
    say the rocklike name
    of your ardent-rock nature
    And it cannot say it,
    its faceless body cannot hold
    a pin of lips, but I know its name:
    rock, I say,
    and it starts to soften.
    Even the word rock does not come from the rocks.
    The word is harder than the rock,
    it cracks the rock open,
    it is the armed reflection which knows it is an image
    compassionate water of that which it reflects.
    True, the word comes from the poet.
    The word rock

is not a marble creature
and it does not come from man in the same way
in which the bird seems an invention of the tree.
The world of the poet
does not grant any suffrage
Even to the loftier rocks.
But the world without rocks of the poet
originates, however, from the world of the rocks
- Eduardo Lizalde
(Translation: Adriana Menassé)

These behavioral coordinations in which we live create a world of objects that appear in "languaging". In other words, "the human being exists in language, in which our behavioral coordinations shape our human world, our internal world with its concepts, its abstract thoughts, symbols, mental representations and self-consciousness" [8].

As we can see in this essay, the "language" about *specificity* have created room for diverse and contradictory observations. But not only language permeates our perceptions of a specific reality; vision is another factor that plays a central role in this filtering of the world, for "we do not see the 'space' of the world, we live our visual field" [8].

24. Rationalistic logic is a unidimensional, casual and deterministic perspective which, in most cases, reduces the phenomena under study to a linear causality; for this reason, Edgar Morin and other thinkers use the epistemological concept of dialogic instead of Aristotelian logic. In dialogic, a complex association (complementary/concurrent/antagonistic) of required instances, which are jointly necessary for the existence, functioning and development of a complex phenomenon, is accepted. A well-known example of this perspective is the double nature, corpuscular and ondulatory, of quantum particles [16], which implies a dialogic but is incompatible with logic.

25. The phenotype, which is a part of organismic totality, may have a complex functional role in the evolution of organisms [14]. We have denominated this epigenic perspective of the phenotype as epiphenetic, seeking thus to express the generative process of a living being emphasizing the role of the phenotype in its dynamics of auto-eco-organization, an even to encoding inheritable information [38, 84, 121, 123, 124].

26. It is fundamental to keep in perspective that the auto-eco-poietic unity of living things indicates that a stimulus is not something "foreign" that comes from extraneous and fortuitous surroundings; on the contrary, the "auto-eco-stimulus" is an articulate and dynamic part of this structural-functional unity.

27. Evidence coming from the molecular organization perceived in complex phenomena, such as cellular energetic efficiency, vectorial biochemistry, the induction of organizational patterns and even biofield-mediated processes, among others, indicates that both the molecular and the organismic phenotypes know and constantly modify their environment. Much of this cognition can be codified and even transmitted complementarily to that corresponding to the conventional genome. [22, 51, 112, 117, 137, 139, 141, 143, 145-147, 154, 155, 187-191].

28. This filter in perception restricts our liberty by riveting knowledge to a certainty. Certainties place us in a space where communication with what is perceived becomes suspended, thereby blocking the incorporation of experiences as an effective means of comprehending the phenomenon of knowledge [8].

Although we have spoken of a knowledge that is in constant construction and is of an autopoietic nature, it should be kept in mind that its formation also implies a dominion of memory. "It is a question of statements which are no longer admitted or discussed, which therefore define neither a body of truths nor a dominion of validity; but rather concerning which relationships of filiations, genesis, transformation, continuity and historical discontinuity are established" [180].

This life's five windows of the soul
Distort the heavens from pole to pole
And lead you to believe a lie
When you see with, not through, the eye.
- William Blake

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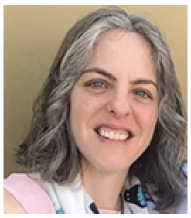

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