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Modeling a Semiotic Process in the Immune System: Signal Transduction in B-cells Activation

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Abstract. Here, we present a semiotic model of signaling pathways in B-cells in order to substantiate the view that semiotic modeling is required for the referential aspect of signaling processes to be grasped. We discuss how a process of asymmetry-formation through membrane closing puts living systems under selection pressure to develop semiotic competence, and, thus, signaling becomes a key process in the interface between system and environment. We introduce a number of notions in Peirce's theory of signs, giving emphasis to the explanation of semiosis as a dynamic process in which chains of triads are instantiated, and develop a semiotic model of signaling pathways in B-cells based on those notions. We offer new, semiotic tools to model signaling in living systems, explaining how the relation to the same external object is maintained throughout several changes in the material bases of signaling (*i.e.*, signs) in such systems.

Keywords: Semiotics, Peirce, Signaling, Modeling, Information.

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1 Introduction

'Signaling' has become in the last decade a central concept in biological thought. This seems quite natural when we think of biology as an informational science, as 'systems biologists' now propose (Ideker et al. 2001). Biology has been increasingly conceptualized as a communication and information science, even though it is not clear at all what is meant by 'information' in biology (Griffiths 2001, Jablonka 2002, Jablonka & Lamb 2005). It is now quite evident that biological information operates at multiple hierarchical levels, in which complex networks of interactions between components are the rule. Consequently, the understanding of the structure and dynamics of entities and processes in living systems demands that they are located in complex informational networks and pathways (Ideker et al. 2001). Moreover, living systems should continuously communicate with each other, and, also, respond to cues from the environment in regular ways. We believe that Peircean biosemiotics can play an important role in this new wave

of biological research, by offering new conceptual and methodological tools for building models of informational and communicational processes in living systems.

The concept of 'information' can be seen as an open problem in biology, since this science lacks a semantic and pragmatic account of information in living systems (Griffiths 2001, Jablonka 2002, Jablonka & Lamb 2005). We think it is fair to pose a similar problem with regard to 'signaling', since it may be currently regarded as little more than a metaphor, since it does not acquire its meaning from a clear theoretical framework that explains how signs are produced, communicated, processed, interpreted by living systems. It is true that we have detailed accounts of several signaling pathways and networks, including a multitude of molecules participating in intracellular signaling routes. This increasingly complex picture of signaling events in cellular systems led to the appearance of databases and wall charts showing several intracellular signaling pathways and networks in cells (*e.g.* Matys et al. 2006). Nevertheless, as we obtain more and more information about signaling pathways, we face an increasing danger of losing from sight common organizational, functional, and also semiotic aspects in these pathways. To build a proper theoretical understanding of signaling, one needs to comprehend how molecules can act as signals, and, thus, mean something else to the cell than just the molecules they are in themselves. How can molecules be signs that stand for something else, say, a virus-infected cell, a prey, an internal state of an organism, and so on? Our view is that semiotic models are required for the referential aspect of a signaling process to be grasped. In this paper, we discuss a semiotic model of signaling pathways involved in B-cell activation in order to substantiate this view.

2 Semiotic closure in cellular systems and the necessity of signaling

Based on a characterization of living systems as measuring devices, Pattee (1982) argues that they need self-referentiality. He suggests that a system must have a function, if it is to qualify as a measuring device, and he adds that the most primitive concept of a function implies the improvement of an organism's fitness. When it acts as a measuring device, a living system is at the same time establishing an epistemic cut separating itself, as an observer, from its environment. Hence, as Hoffmeyer states, "measurement and observer are epistemic concepts and as such they presuppose at least an organisation that can construct the measuring device and use the results for its survival" (Hoffmeyer 2001: 124). This is what Pattee (1982) has called the semantic closure principle, a vital property that emphasizes the self-referential dimension of the living and is accepted by many researchers (e.g. Hoffmeyer 2000, 2001; Etxeberria and Moreno 2001) as a necessary condition for differentiating living from non-living systems. But how can we legitimate the semantic closure property and how is it related to the notion of signaling?

Actually, the property of semantic closure and the resultant semantic cut cannot justify the origin and evolution of the living (Hoffmeyer 2000, 2001). As stated above, semantic closure implies a separation between the system and its environment. The problem is that this separation should be raised from within the system, instead of being postulated by an observer. Therefore, Hoffmeyer (2001) decides to follow the 'no cut' position, which sees the emergence of life as an instantiation of more general dispositions that characterize our world. Hence, he has argued in favor of "a process of asymmetry-formation through membrane closing" as "a key to a theory of the origin of life, or subject-ness" for any living system (Hoffmeyer 1998: 34). Indeed, the semantic closure property cannot be developed without a closed membrane separating the world into two unequal parts: an internal and an external part. As Hoffmeyer states, one should not forget that the asymmetry between organism and environment is an asymmetry between "the membranes' excluded outside and its excluded inside" (Hoffmeyer, 2001: 125). Initially, this asymmetry has a spatial or topological nature. Hence, closure through membrane formation, which sometimes is referred to as "topological closure" (Hoffmeyer 2001: 124), functions as a way to reduce or filter out the variety of the environment by pointing out a certain external space of interest that may be potentially internalized, and also as an indicator of the internal part of the system that can be externalized, and conse-

quently be an extension of the system into the environment. From this perspective, one should consider the origin of an interaction between a system and its environment as inseparable from the origin of both the respective system and the environment. Therefore, we may safely consider that the reason why living systems were selected for using signaling lies in the event that at a certain moment in their evolution they got a membrane separating its internal medium from the external environment.

The important question to be answered at this point is what is the difference between the way systems closed by membranes, exhibiting the property of semantic closure, interact with their environments, and the way other non-observing systems react to their circumstances. Why cannot we model all these interactions, no matter if we are talking about living systems or not, as mere physical interactions, understandable, without remainder, by modeling the molecular events constituting a signaling process? The situation seems to be much more complex. The closure of a system through a semi-permeable membrane is what permits the system to develop a closed dynamical organisation, where the constraints of its supporting structure acquire an informative nature within a self-referential and recursive context. As Etxeberria and Moreno argue (2001), this dynamical process gives rise to the semantic closure of the living system which in a sense accounts for its partial independence of external environmental control. Hence, in this case, we should not talk of a mere interaction based on physical properties, but rather of communication between a system and its environment. Since an asymmetry between a system and its environment is vital for the former to become a living entity and a membrane accounts for the maintenance of this asymmetry, then the whole interaction is taking place through the membranes. Specially, the abovementioned communication, as every communication between living systems, has not just an informative, but also an interpretive dimension, which emerges from the looping of other-reference (made possible through the topological closure through membrane-formation) into self-reference. Hoffmeyer (1998, 2000, 2001) calls the formation of this feedback link a semiotic closure.[b] He also argues that this is a decisive step for the system's understanding of its environment really matters to the system itself.

Consequently, a membrane should be considered as a dynamical interface between a living system and its environment, and signaling as the key process in this interface, allowing signs to be communicated and interpreted between compartments. For such semiotically closed, or even more precisely, for self-referential systems that exhibit code-duality (Hoffmeyer and Emmeche 1991) and interpret their environments in an open-ended fashion, communication through signaling becomes a fundamental process for satisfying their internal aims and future-oriented scopes and goals. From this perspective, living systems are able to answer to environmental cues in a regular, lawful way, despite the fact that they are closed, that they have boundaries. They are able to interpret signals of their environment in a way that will best serve their functions. The essential notion with regard to a living system's purposeful interaction with the environment is the one of 'reference', since an organization should be created inside the system that will refer to something outside the system in such a way that the internal processes will be functionally adjusted to the environmental conditions. In such circumstances, the system is under selection pressure to develop semiotic competence, which cannot be accounted for in a satisfactory way without considering both the system's capacity for making distinctions and an interface linking the interior and the exterior. The living system has to be able to internalize somehow cues that inform it about the environment, producing signs inside itself which refer to the same thing or process to which the external cue referred to. The basic idea, then, is that the same relationship an external sign has to a given object (a thing or process) will be

[b] Although Hoffmeyer (2000) suggested that semiotic closure should not be confused with semantic closure, the latter may be considered a logical consequence of the former. Actually, in Hoffmeyer's scheme, semiotic closure initiates through the establishment of the capability for other-reference, mainly, through the formation of a semi-permeable membrane and the analogically-coded interaction of the system. The formation of symbolic reference in the form of digital records emerged from the already established analogically-coded referentiality, or as Hoffmeyer states "digital codes grew out of analog codes, not vice versa" (Hoffmeyer 2001: 129). In other words, there has been an interpreting machinery that created and stored some constraints, which are functionally expressed, and on which the analogically-coded structures of the interpreting machinery depend. These constraints cannot act outside the interpreting machinery, hence, the semantic closure.

preserved when an internal sign is produced. This is the basis of a process we call here 'referentiality'. An internal sign will refer to, or stand for, the object in the same way as an external sign refers to, or stands for it. In order to model this relationship, we take as a basis Peirce's theory of signs. This signaling process primarily aims at the maintenance and evolution of the living system's semiotic closure and consequent measuring capacity and is, as Hoffmeyer (2001) argues, not understandable from pure biochemistry, since it requires the recognition of biochemical events as traces or measuring marks, and this, in turn, indicates the need for semiotic analysis, not just a physicochemical one.

3 Some basic ideas in Peirce's theory of signs

We will ground our approach to signaling on a well-developed theoretical framework to account for sign processes developed by Charles S. Peirce. Several authors, such as, for instance, Pietarinen (2005), Freadman (2004), Hookway (2002), Bergman (2000a, b), Deacon (1997), Fetzer (1988, 1997), Houser et al. (1997), Noble & Davidson (1996), Hoffmeyer (1996), Emmeche (1991), and Ransdell (1977) propose that the semiotics of C. S. Peirce offers powerful tools for the investigation of meaning, language and communication. It is clear to us, however, that a framework built in the turning of the 20th century should be complemented and adjusted in order to account for the wealth of knowledge we now have about signaling in living systems. We are not claiming, thus, that signaling can be explained solely on the basis of Peirce's theory of signs, but only that this theory brings important contributions to the understanding of referentiality in this process, potentially leading to a deeper and more precise explanation of what signaling is, and, furthermore, to new insights into the functioning of signaling pathways and networks.

In this paper, we will focus mainly on the explanatory task described above. We need, first, to introduce some basic ideas in Peirce's theory of signs. Then, we will apply these ideas to model signaling processes in B-cell activation, from antigen binding to receptors in the cell surface to changes in the intracellular milieu mediated by signaling processes and leading to a different phenotype, amounting to the activation of B-cells. In doing so, we are expanding on a modeling approach we sketched in a previous paper (Queiroz & El-Hani 2006).

It is important to keep in mind from the very start that we will just present a small number of basic notions in Peirce's theory. We refer those who want a more detailed and deeper presentation to Peirce's original works.

For Peirce, a sign is something that stands for something else than itself. In our modeling of the B-cell receptor (BCR) signaling pathways, for instance, an antigen will be treated as standing for something else than itself, say, a virus-infected cell, which a B-cell can detect in its environment by using antigens as signs referring to it. Peirce defined signs in several different ways (Marty & Lang 1997), but we will refer here to just some basic definitions which will be useful in our work. He conceived a 'Sign', for instance, as a 'First' which stands in such a genuine triadic relation to a 'Second', called its 'Object', so as to be capable of 'determining a Third', called its 'Interpretant', to assume the same triadic relation to its Object in which it stands itself to the same Object (CP 2.274. See also CP 2.303, 2.92, 1.541).[c] When Peirce defines a sign in this way, he already hints at the way a sign acts, making it clear that it is something that stands for something else, its object, in such a way that it ends up producing a third element, an interpretant, which is the effect a sign produces on an interpreter. In signaling systems, sign interpretation typically results in a new sign within the interpreter, which refers to the object as the former sign refers to itself, or ultimately in an action, which can lead to the termination of a signaling process. We have to deal, thus, with a triadic relation, through which an external sign stands for an object in such a manner that it pro-

[2] We follow here the practice of citing from the *Collected Papers of Charles Sanders Peirce* (Peirce, 1931-35, 1958) by volume number and paragraph number, preceded by 'CP'. Readers interested in Peirce's original works should also check *The Essential Peirce* (EP).

duces another sign that stands for the object in the same way as the external sign stands for it. In our view, this is precisely the kind of relation we should consider in order to model signaling, and, particularly, referentiality in signaling processes, within a consistent theoretical framework.

That the interpretant, for Peirce, is another sign, created by the action of a previous sign, is clear in the following statement: A sign is "anything which determines something else (its interpretant) to refer to an object to which itself refers (its object) in the same way, the interpretant becoming in turn a sign, and so on, ad infinitum" (CP 2.303. Emphases in the original). Accordingly, it is important to bear always in mind that the interpretant is not necessarily the product of a process which amounts to 'interpretation' in the sense we use this term to account for human cognitive processes. As explained above, the fundamental character of the interpretant is that it is a new sign produced by the action of a previous sign in such a manner that both share the same referent.

The semiotic relation (i.e., the relation between sign, object, and interpretant) is regarded by Peirce as an irreducible relation, in the sense that it cannot be resolved into interactions between pairs (sign-object, or sign-interpretant, or interpretant-object). This triadic relation was named by Peirce 'semiosis', and corresponds to the action of a sign. That is, a sign only acts through the establishment of a triadic relation with its object and a new sign it creates, its interpretant.

For the sake of our arguments, we should also consider a distinction between two kinds of objects proposed by Peirce. He distinguished between the immediate and the dynamical objects of a sign. The dynamical object is something in reality which by some means contrive to determine the sign to represent it (CP 4.536). The aspect of the dynamical object which is represented in the sign is the immediate object, which amounts, thus, to the dynamical object in its semiotically available form (or, else, the object as the sign represents it). The sign does not represent the dynamical object in its reality, but just indicates that object. The system which is causally affected by the sign (because it stands for something else to that system) should establish what is the dynamical object indicated by the sign through processes which have been selected for in the evolutionary history of that kind of system. In the ontogenetic timescale, the system will acquire its semiotic competence, i.e., its competence as a sign interpreter, through development. In a number of semiotic systems, the development of semiotic competence will be a 'closed' process, in the sense that it is hardwired in the biological structure of the system, and cannot be modified by experience. In the case of cellular interpreting systems, this is the typical case (Weber et al. 1989, Hoffmeyer 1998, 2001), and it is the developmental result of the feedback loop between DNA and environment, which has been called above semiotic closure. Nevertheless, there are also 'open' processes of semiotic competence development, such as those observed in animals which learn from experience.

It is clear from the above explanation that a system which is successful in establishing what the dynamical object of a sign is does not capture in any sense the reality of that object; rather, to establish what a dynamical object is simply means to subsume it under a general class of events, processes, or entities, and, thus, be able to answer to it in a regular way, learnt by living systems through evolution and development (i.e., by evolutionary and somatic learning, when the latter is available to the system).

Systems which are capable of producing, communicating, receiving, and interpreting signs are called by Fetzer semiotic systems: "What makes a system 'semiotic' thus becomes that the behavior of the system is causally affected by the presence of a sign because that sign stands for something else […] for that system" (Fetzer 1997: 358). As we argued above, living systems evolved as semiotic systems due to the presence of a membrane separating its internal medium from the external environment, and, due to their semiotic closure, they have to internalize cues about their environment (signs) by producing new signs (interpretants) inside itself so as to make them refer to the same thing or process to which the external sign referred to. In our modeling approach, we will systematically conceive of B-cells as semiotic systems (as, indeed, all cells are, according to our approach).

Semiosis necessarily entails the instantiation of chains of triadic relations (which we will abbreviate here as 'triads'), since a sign in a given triad will lead to the production of an interpretant, which is, in turn, a new sign. Therefore, an interpretant is both the third term of a previous triadic relation and the first term (sign) of a subsequent triadic relation (Savan 1986. See Figure 1). Here, we have a first transition accounting for the dynamical nature of semiosis, namely, the interpretant-sign (I-S) transition. By this 'transition' we simply mean that the same element that plays in a triad the role of the interpretant will play in a subsequent triad the role of the sign. After all, from a Peircean perspective, to perform sign processing and interpretation is to produce further (or, as Peirce says, more developed) signs.

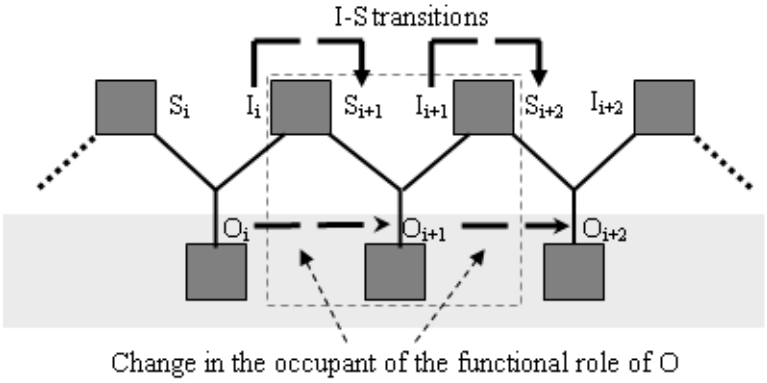

Figure 1: The triadic relation forms a chain of triads. The grey area at the bottom of the figure shows that all signs in the chain of triads refer to the same dynamical object through a series of immediate objects. The arrows show the interpretant-sign (I-S) transition and the changes in the occupant of the functional role of the immediate object.

When the I-S transition takes place, there is also a change in the occupant of the functional role of the immediate object. When the interpretant becomes the sign of a new triad, the relation of reference to the same dynamical object depends on the fact that the new occupant of the role of immediate object stands for the same aspect of the dynamical object that the immediate object of a previous triad stood for. As Figure 1 shows, in a triad ti a given sign S_i indicates a dynamical object by representing some aspect of it, the immediate object O_i. Through the triadic relation, an interpretant I_i is produced inside the semiotic system. This interpretant becomes the sign in a subsequent triadic relation, S_{i+1}, which now indicates the same dynamical object. It should indicate that object through a new immediate object, which corresponds to an aspect of the dynamical object represented in the sign. We have now a new occupant of the role of immediate object that stands for the same aspect of the dynamical object which was represented in the previous sign, S_i. It is in this sense, then, that there is a change in the occupant of the functional role of the immediate object, from O_i in a previous triad to O_{i+1} in a subsequent triad. Through the triadic relation, a further interpretant, I_{i+1}, will be produced, which will then become the sign in a new triad, S_{i+2}, and thus successively, up to the end of that specific sign process. This typically amounts to the triggering of an action, which is the final interpretant in this semiotic process, usually leading to its termination.[d] These ideas will become increasingly clear as we proceed with the analysis of BCR signaling pathways.

4 Modeling signaling pathways in B-cells

The B cell antigen receptor (BCR) is a multiprotein complex consisting of a membrane-bound immunoglobulin molecule (mIg), the ligand-binding part, and an Ig-α/Ig-β heterodimer associated with mIg, which acts as a signaling subunit and couples the receptor to intracellular signal transducer elements (Reth & Wienands 1997). BCR has two functions in B-cell activation (Pierce 2002): it initiates signaling pathways

[3] The way we use the concept of 'final interpretant' in our analysis will become clearer as our argument proceeds. In the last section of the paper, we will explain in more detail how we use this concept.

that result in a series of intracellular actions in B-cells, including changes in gene expression patterns, which lead, in turn, to the activated B-cell phenotype; and it plays a role in the uptake and processing of antigens to be presented to T-helper cells, which will assist B-cells in achieving full activation (Figure 2).

If the series of mechanistic interactions which take place in a signaling pathway is to be regarded as a signal transduction, something more than just molecular interactions should take place. It is not that some additional element, besides the molecules itself, should be added to the compositional aspect of the signaling pathway; rather, what should be added to the picture is the kind of relation explained above, a semiotic relation by means of which a molecule such as an antigen can be a sign that stands for something else, say, a virus-infected cell, and, in turn, lead to the production, within the living system, of other (signaling) molecules which stand in the same relation to that object in which the antigen itself stood. Only in this manner we will be able to explain not only the molecular interactions in a pathway, but also its referentiality, which is a fundamental property to account for, if we want to explain why this is a signal transduction process.

Let us take a closer look at initiation events at the BCR signaling system. Figure 3 presents a model of the main events at stake. In resting B cells, BCR is excluded from membrane domains (lipid rafts) which concentrate the transducer, *Lyn*. In the absence of antigen, the BCR monomer has a weak affinity for lipid rafts, but antigen binding makes BCR molecules associate with each other, increasing affinity for the domains. Stable residency in the domains results in association with *Lyn*, which phosphorylates BCR, initiating several signaling pathways. In the figure, another kinase, named *Syk*, which initiates one of the signaling cascades resulting from BCR activation, is shown.

The production of an interpretant inside the B-cell, in response to antigen binding to mIg, is triggered by the mIg-associated Ig-α/Ig-β heterodimer, the signaling subunit of BCR, which couples the receptor to *Lyn*, by means of phosphorylation reactions. Signal processing depends, indeed, on the activation of diverse protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). In the cytoplasmic tail of both Ig-α and Ig-β proteins, we find an immune receptor tyrosine-based activation motif (ITAM), which interacts with different signaling elements and is required for signaling. The ITAM has two tyrosines which can be phosphorylated, and this can control their mode of association with other signaling elements (Reth & Wienands 1997). In turn, the dephosphorylation of pITAM by PTPs may restore the resting state of the BCR. In sum, the ITAM plays a crucial role in the signaling pathways initiated by antigen-binding in resting B cells, triggering the signaling response by coupling the BCR to transducer elements.

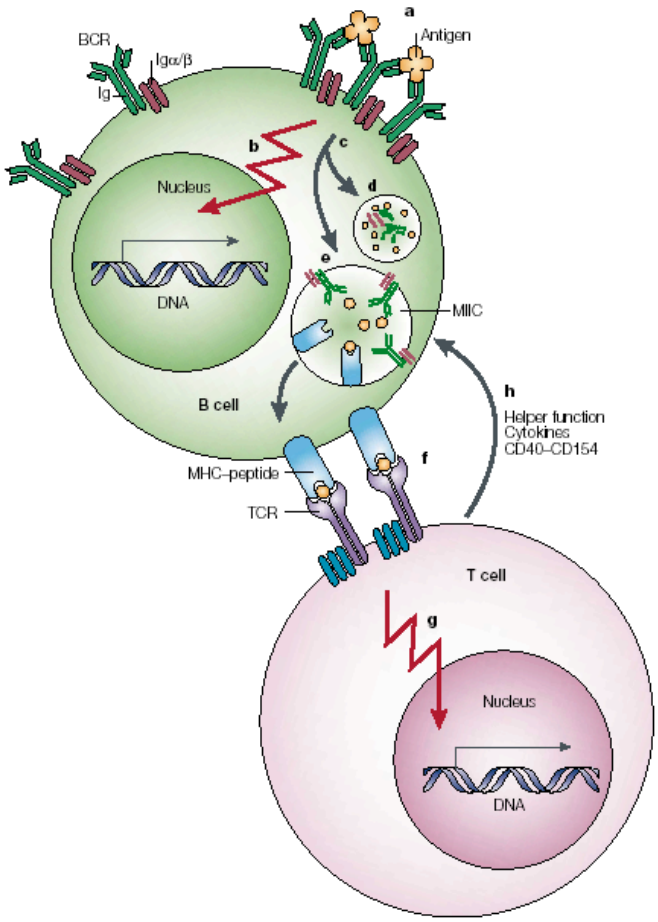

Figure 2: The functions of BCR in B-cell activation. Following antigen binding (a), the B-cell receptor (BCR) triggers signaling pathways, which (b) regulates, for instance, the transcription of genes associated with B-cell activation. BCR is internalized (c) and either degraded (d) or trafficked to an intracellular compartment (MIIC) (e), where complexes containing the antigen bound to BCR are formed. These complexes are transported to the cell surface, where they are recognized by the T-cell receptor (TCR) of T-helper cells (f), leading to T-cell activation (g), by triggering other signaling pathways. The activated T cell provides 'help' to the B cell, leading to full B-cell activation (h). Ig: Immunoglobulin. (From Pierce 2002).

An antigen is a sign which stands for something else, say, a virus-infected cell, and BCR acts as an interpreting system in the cell membrane, triggering processes by means of which new signs, i.e., interpretants, are produced inside the B-cell. The first intepretant in this case is the phosphorylated state of BCR, which is a sign that stands for the virus-infected cell as the antigen itself referred to it. This generates a new triad, linked to the previous one by the double role played by the phosphorylated state of BCR, which is both the interpretant of a first triad, and a sign of a second triad. We are dealing with the I-S transition, a basic process underlying the generation of chains of triads. When the I-S transition takes place, the aspect of the virus-infected cell which was represented in the antigen (O_i) has come now to be represented in the phosphorylated state of BCR (O_{i+1}). To put it differently, following the I-S transition, there is a change in the occupant of the functional role of O (Figure 4). It is this latter change that makes it possible that the same entity or process is kept as a stable referent throughout the signaling process, despite the several changes in the material bases of signaling, i.e., in the signs involved.

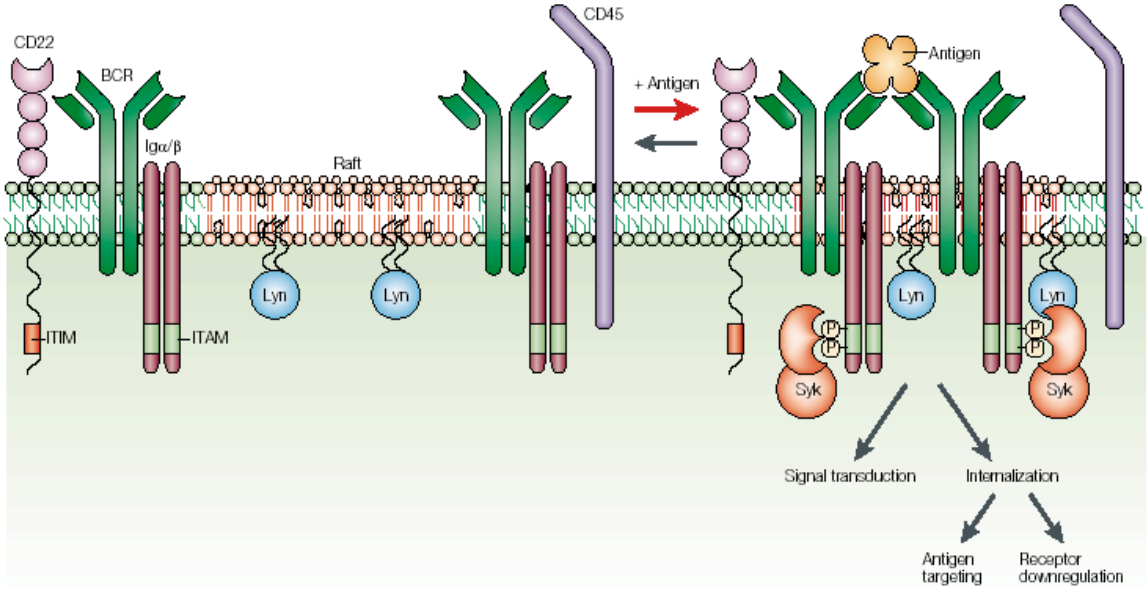

Figure 3: Model of the initiating events in the signal-transduction cascades leading to B-cell activation. (From Pierce 2002).

Biochemical and genetic evidence has shown that *Syk* has a key role in a well-defined pathway of B-cell activation, related to the release of Ca^{2+} from the endoplasmic reticulum (Reth and Wienands 1997). In this case, the binding of *Syk* to the phosphorylated BCR makes a specific interpretative process proceed. When *Syk* is activated, it leads to the activation of another enzyme, phospholipase Cγ (*PLC-γ*), which is an effector, converting the membrane component phosphatidylinositol 4,5-biphosphate into the two second messengers diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). This illustrates a case of divergence of intracellular signals, modeled in semiotic terms by means of the production of more than one interpretant from a single sign, namely, the phosphorylated state of BCR.

DAG remains attached to the inner side of the plasma membrane and recruits and activates the cytosolic protein kinase C (PKC). IP3 binds to receptors on the endoplasmic reticulum, causing the release of CA^{2+} ions. The release of CA^{2+} ions is one of the final interpretants of the signaling pathway managed by *Syk*. The number of different PKC substrates (for example, CD20, c-Raf, IκB) and the multifunctional role of Ca^{2+} ions on cell metabolism make it clear how an original sign-response can be broadly diversified by the signaling systems of a cell.

DAG and IP3 stand for the virus-infected cell in the same way as the antigen and the phosphorylated state of BCR stood, maintaining the reference of the signaling process through the changes of occupants of the functional role of the immediate object. IP3, for instance, acts as a sign to a subsequent triad, triggering the production of the final interpretant mentioned above. In these terms, signal-transduction cascades can be modeled as particular semiotic processes, interpreted in accordance with our model as chains of triads that indicate the same dynamical object throughout.

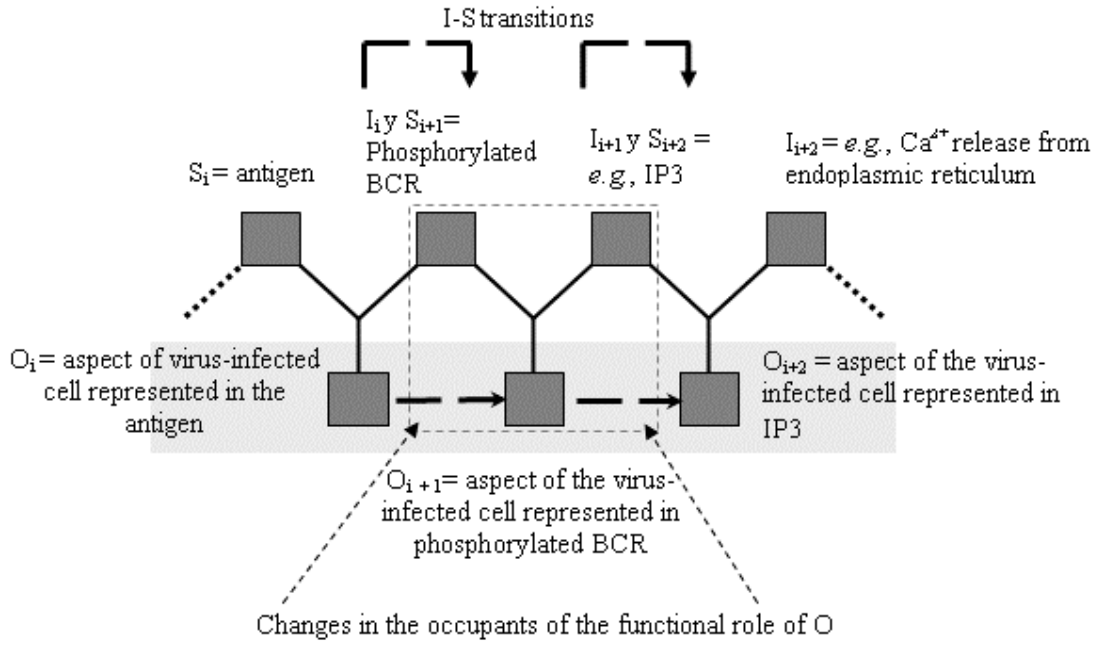

Figure 4: A model of one of the signaling pathways triggered by activated BCR as a chain of triads. Notice the I-S transition and the changes in the occupants of the functional role of O. Referentiality in a signaling pathway is modeled in terms of these changes of occupants, which show how the reference to the same external entity or process is maintained throughout the signaling process.

From a global perspective, the overall result of the semiotic process modeled above can be grasped in terms of a triad containing the antigen as a sign, the virus-infected cell in its semiotically available form (as represented, say, in the three-dimensional form of the antigen) as an immediate object, and, in the case of the signaling pathway modeled above, Ca^{2+} release as the interpretant (Figure 5). This is an indexical sign process, since the antigen (as a sign) and the virus-infected cell (as the object of that sign) are connected through a physical (indeed, causal) correlation. As Peirce defined it, "an Index is a Sign which refers to the Object that it denotes by virtue of being really affected by that Object" (CP 2.248) (For more details on the classification of signs as icons, indexes, and symbols, see Queiroz & El-Hani 2006).

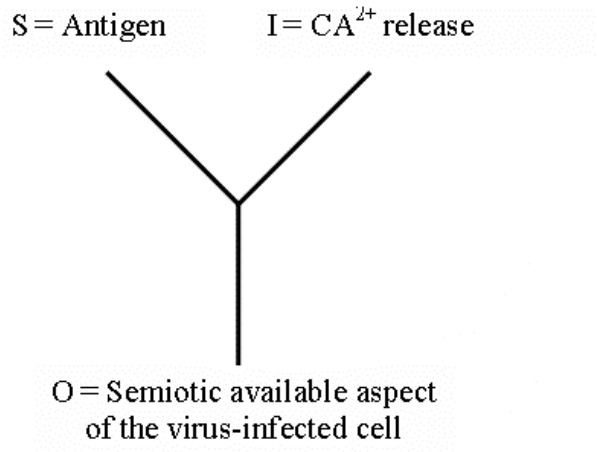

Figure 5. A global semiotic analysis of a semiotic process triggered by antigen-binding to BCR.

5 Concluding remarks

As Reth and Wienands (1997: 472) stress, to answer questions about signaling systems, it is necessary to develop new tools. They mention, in particular, the requirement of better definitions of signaling elements and the development of computer models of signaling systems. We would like to add that it is also important to answer how the relation to the same external object, say, a virus-infected cell, is maintained throughout several changes in the material bases of signaling (i.e., signs) in cell systems. This question demands a theory of signs, and we intended to show in this paper that Peirce's theory offers powerful grounds for developing an explicit and formal treatment of referentiality in signaling pathways.

We believe semiotic modeling is a necessary counterpart of functional and mechanistic models of signaling systems, given that the maintenance of referentiality is clearly a fundamental feature of signal transduction. We need to explain how signaling molecules play their roles of being signs for something else (and, above all, for the same dynamical object) throughout signaling pathways. In order to explain how this is possible, we modeled signaling pathways managed by *Syk* in the BCR signaling system as chains of triads at the focal level, established by the I-S transition. In particular, the change in the occupant of the functional role of O, due to the I-S transition, explains how the relation to the same dynamical object can be maintained throughout sign processing.

To stress the necessity of semiotic modeling of signaling processes, we can ask why molecules such as DAG and IP3 can be called 'second messengers'? What is the message and how is it preserved in them? The message refers to the presence of a non-self entity, for instance, a virus-infected cell, within the organism. But how is the reference to such an entity preserved in the 'messengers'? In order to successfully model the maintenance of reference throughout the process we should go beyond the pairwise or dyadic interactions between molecules and their substrates, and build a semiotic model capable of showing how the reference to a non-self entity external to the cell can be maintained during the processing of signals within the cell. A semiotic analysis allows us to go beyond a metaphorical usage of the expression 'second messenger': DAG and IP3 are second messengers precisely because they are interpretants produced as a result of the processing of an extracellular sign (a 'first messenger'), in this case, an antigen. In turn, the changes in the occupants of the functional role of O in chains of triads corresponding to the signaling pathways managed by *Syk* show how the reference to the virus-infected cell is maintained while the material bases of the message, namely, the signs, keep changing throughout the process.

The reception, processing, and interpretation of signs in living systems are characterized by their regular and lawful nature. That is, they follow habits acquired by living systems through evolution and development. One of the main features of processes based on habits is that they are teleological, being 'teleology' here understood, in Peircean terms, as a characteristic of processes which tend toward a final state. The final interpretant in a semiotic process is the final state of this process, which amounts to a tendency to be realized when a given chain of triads is triggered, but is not determined or bound to happen, since other final states can follow from the semiotic process, as in the case, for instance, of misinterpretation. In a signaling pathway, interpretation typically leads to an action performed by an effector, such as phospholipase Cγ, in response to the processing of a sign in a signaling pathway. This action ranges from cytoskeletal reorganization to a change in gene expression patterns to the release of some substance, and so on, as we showed in our analysis of the role of PLC-γ in the BCR signaling system.

In sum, we believe the semiotic modeling of the BCR signaling system put forward in this paper shows how biosemiotics allows us to advance in the construction of models of informational and communicational processes in living systems, such as signaling. This is clearly a relevant task in current biology, which has been described as an informational science (Ideker et al. 2001) but lacks a consistent theoretical framework to make notions such as 'information, 'code', 'signaling', etc. go beyond mere metaphorical usage (e.g. Emmeche & Hoffmeyer 1991, Griffiths 2001, Jablonka 2002, Jablonka & Lamb 2005, Queiroz et al.

2005, El-Hani et al. 2006). In a previous paper, we proposed a definition of 'information' as "a triadic-dependent process through which a form embodied in the Object in a regular way is communicated to an Interpretant through the mediation of a Sign" (El-Hani et al. 2006: 16; Queiroz et al., 2005: 65). If we now put together this semantic/pragmatic definition of information with the analysis of signaling presented here, it will become clear how signaling is a process of communicating information about a dynamical object (say, a virus-infected cell) to the internal medium of a cell, allowing it to answer in a regular, lawful way to that object.

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