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The Biosemiotic Approach in Biology: Theoretical Bases and Applied Models

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Biosemiotics is a growing field that investigates semiotic processes in the living realm in an attempt to combine the findings of the biological sciences and semiotics. Semiotic processes are more or less what biologists have typically referred to as "signals," "codes," and "information processing" in biosystems, but these processes are here understood under the more general notion of *semiosis*, that is, the production, action, and interpretation of signs. Thus, biosemiotics can be seen as biology interpreted as a study of living sign systems—which also means that semiosis or sign process can be seen as the very nature of life itself. In other words, biosemiotics is a field of research investigating semiotic processes (meaning, signification, communication, and habit formation in living systems) and the physicochemical preconditions for sign action and interpretation.

To treat biosemiotics as *biology interpreted as sign systems study* is to emphasize an important intertheoretical relation between biology as we know it (as a field of inquiry) and semiotics (the study of signs). Biosemiotics offers a way of understanding life in which it is considered not just from the perspectives of physics and chemistry, but also from a view of living systems that stresses the role of signs conveyed and interpreted by other signs in a variety of ways, including by means of molecules. In this sense, biosemiotics takes for granted and preserves the complexity of living processes as revealed by the existing fields of biology, from molecular biology to brain science and behavioral studies. However, biosemiotics attempts to bring together separate findings of the various disciplines of biology (including evolutionary biology) into a sign-theoretical perspective concerning the central phenomena of the living world, from the ribosome to the ecosystem and from the beginnings of life to its ultimate meanings. From this perspective, no positivist (i.e., theory-reductionist) form of unification is implied, but simply a broader

approach to life processes in general, paying attention to the location of biology between the psychological (the humanities) and the physical (natural) sciences.

Furthermore, by incorporating new concepts, models, and theories from biology into the study of signs, biosemiotics attempts to shed new light on some of the unsolved questions within the general study of sign processes (semiotics), such as the question about the origins of signification in the universe (e.g., Hoffmeyer 1996), and the major thresholds in the levels and evolution of semiosis (Sebeok 1997; Deacon 1997; Kull 2000; Nöth 2000). Here, signification (and sign action) is understood in a broad sense, that is, not simply as the transfer of information, but also as the generation of the very content and meaning of that information in all living sign producers and sign receivers.

Sign processes are thus taken as real: they are governed by regularities (habits, or natural rules) that can be discovered and explained. They are intrinsic in living nature, but we can access them—not directly, but indirectly through other sign processes (e.g., scientific measurements and qualitative distinction methods)—even though the human representation and understanding of these processes in the construction of explanations is built up as a separate scientific sign system distinct from the organisms' own sign processes.

One of the central characteristics of living systems is the highly organized character of their physical and chemical processes, partly based upon informational and molecular properties of what has been described in the 1960s as the genetic code (or, more precisely, organic codes). Distinguished biologists, such as Ernst Mayr (1982), have seen these informational aspects as one of the emergent features of life, namely, as a set of processes that distinguishes life from everything else in the physical world, except perhaps human-made computers. However, while the informational teleology of computer programs are derived, qua being designed by humans to achieve specific goals, the teleology and informational characteristics of organisms are intrinsic, qua having evolved naturally, through adaptational and evolutionary processes. The reductionist and mechanistic tradition in biology (and philosophy of biology) has seen such processes as being purely physical and having to do with only efficient causation. Biosemiotics is an attempt to use the concepts of semiotics in the sense employed by Charles Sanders Peirce to answer questions about the biological emergence of meaning, intentionality, and a psychological world (CP 5:484).[1] Indeed, these are questions that are hard to answer within a purely mechanistic and reductionist framework.

The term "biosemiotic" was first used by F. S. Rothschild in 1962, but Thomas Sebeok has done much to popularize the term and the field.[2] Apart from Charles Peirce (1939–1914) and Charles Morris (1901–1979), early pioneers of biosemiotics were Jakob von Uexküll (1864–1944), Heini Hediger (1908–1992), and Giorgio Prodi (1928–1987), and the founding fathers were Thomas Sebeok (1920–2001) and Thure von Uexküll (1908–2004). After 2000, an institutionalization of biosemiotics can be noticed: since 2001, annual international meetings of biosemioticians have been taking place (initially organized by the Copenhagen and Tartu groups); in 2004, the International Society for Biosemiotic Studies was established (with Jesper Hoffmeyer as its first president; see Favareau 2005); the specialized publications *Journal of Biosemiotics* (Nova Science) and *Biosemiotics* (Springer) have appeared; several collections of papers have characterized the scope and recent projects in biosemiotics, such as a special issue of *Semiotica* 127 (1/4) (1999), *Sign Systems Studies* 30 (1) (2002), Sebeok and Umiker-Sebeok 1992, Witzany 2007, and Barbieri 2007.

Also, from the 1960s to the 1990s, the semiotic approach in biology was developed in various branches:

a. Zoosemiotics, the semiotics of animal behavior and communication
b. Cellular and molecular semiotics, the study of organic codes and protolinguistic features of cellular processes
c. Phytosemiotics, or sign processes in plant life
d. Endosemiotics, or sign processes in the organism's body
e. Semiotics in neurobiology
f. Origins of semiosis and semiotic thresholds

Biosemiotics sees the molecular evolution of life and the evolution of semiotic systems as two aspects of the same process. The scientific approach to the origin and evolution of life, partly due to the success of molecular biology, has given us highly valuable accounts of the outer aspects of the whole process, but has overlooked the inner qualitative aspects of sign action, and has led to a reductionist view of causality. Complex, self-organized, living systems are also governed by formal and final causality: formal causality in the sense of the downward causation from a whole structure (such as the organism) to its individual molecules, constraining their action, but also endowing them with functional meanings in relation to the whole metabolism, and final causality, in the sense of the tendency to take habits and to generate future interpretants[3] of the present sign actions.[4] Here, biosemiotics draws also upon the

insights of fields like systems theory, theoretical biology, and the study of complex self-organized systems.

Particular scientific fields like molecular biology, cognitive ethology, cognitive science, robotics, and neurobiology deal with information processes at various levels, and thus spontaneously provide knowledge about biosemiosis (sign action in living systems). Biosemiotics, both as a research program and a general perspective on life, would attempt to integrate such findings, and to build a semiotic foundation for biology. By describing the continuity between body and mind, biosemiotics also helps us to understand the evolution of kinds of mind in living systems, thereby assisting in overcoming some forms of Cartesian dualism that are still haunting the philosophy of mind. In addition, it develops specific models of life processes (such as those proposed here for the genetic information system and signaling systems, discussed shortly), emphasizing their signifying nature, thus helping to enrich and complement the biological sciences as standardly understood.

In what follows, we will draw on Peirce's semiotics to construct two semiotic models: one of the cell's genetic sign system, the other of signal transduction in B cell activation. In this manner, we intend to shed light on the notion of information as employed in the biological sciences.

A Theoretical Basis for a Biosemiotic Approach to Living Systems

The concept of information and related notions in biology should be not only taken seriously, but also clarified by employing appropriate conceptual tools. The use of semiotic concepts and theories to interpret "information talk" can significantly contribute to a precise and coherent formulation of the whole set of notions related to the information concept in biology. A semiotic treatment of biological information can also help to clarify some misunderstandings about the role of genes in biological systems, avoiding much criticized notions such as genetic blueprints and programs (see, e.g., Oyama 2000; Nijhout 1990; Sarkar 1996; El-Hani 1997; Keller 2000), while preserving the concept of biological information, albeit radically reinterpreted. A semiotic approach also lends support to the now widely accepted idea that there is more to information in living systems than just genetic information.

Here, however, our primary aim is to demonstrate how some central notions of Peirce's semiotics can be used to model information processes in biological systems. We will specifically address works in applied semiotics in which we developed analyses of genetic information and signaling systems grounded in Peirce's theory of signs (Queiroz, Emmeche, and El-Hani 2005; El-Hani, Queiroz, and Emmeche 2006; El-Hani, Arnellos, and Queiroz 2007). In other papers, we presented semiotic analyses of communication processes in nonhuman animals (Queiroz and Ribeiro 2002; Ribeiro et al. 2007). The analyses offered here are not, however, the only way to apply semiotics to particular cases. It is important to notice that there are other ways of applying semiotics to biology that are not based on the semiotics of Peirce (e.g., Markoš 2002; Barbieri 2003). As a first step in our argument, we will discuss the status of information talk in biology.

Information Talk in Biology

During the 1950s and 1960s, genetics, cytology, and molecular biology were swamped by terms borrowed from information theory. This "information talk" or "quasi semiotics," still pervades these fields, including widely used terms such as "genetic code," "messenger RNA," "transcription," "translation," "transduction," "recognition," "genetic information," "chemical signals," "cell signaling," and so on. But as the concept of information and its plethora of associated notions were introduced in biology, so were several problems with which the tradition of biology was unprepared to cope. Instead of deepening the discussion about the problems involved in information talk, the trend in the biological sciences was one of treating information as merely sequence information in DNA or proteins.

Some researchers consider information talk as inadequate and merely metaphorical, thus expressing skepticism about the use of the term "information" and its derivatives in biology (Stuart 1985; Sarkar 1996). We disagree with this position, claiming instead that the notion of information and other related ideas grasp some fundamental features of biological systems and processes that might be otherwise neglected. The terms "code," "information," "signals," "message," "signaling," and so on can be seen as necessary to understand the organization of relations in living beings in such a way that makes it clear that what happens in such beings is much more than simple chemistry. Bray, for instance, argues that "organisms can be viewed as complex information-

processing systems, where molecular analysis alone may not be sufficient" (cited by Williams 1997, 476–477). Ideker, Galitski, and Hood (2001), in a paper about systems biology, maintain that biology is an informational science. Indeed, since the early applications of cybernetic models in life sciences, biology has been increasingly conceptualized as a communication and information science (e.g., Keller 2005), even though in many cases it is not clear at all what is meant by "information" in biology (Emmeche 1994; Griffiths 2001; Jablonka 2002; Jablonka and Lamb 2005).

It is not surprising, then, that biologists felt the need to talk about information when delving into the molecular microstructure of living systems. Life scientists needed a way of conveying the idea that more than just physics and chemistry is going on there. Even though all cellular processes are physicochemical processes, they are *complexly organized* physicochemical processes interwoven in communication and information networks. In this context, it is quite difficult to see what would be the real advantage of stripping away information talk from biology, instead of making it more precise and exploring its consequences in more depth. Thus, the problem is not getting rid of information talk, but rather clarifying it by using an appropriate theoretical framework.

As Griffiths (2001) summarizes the problem, genetic information is a metaphor in search of a theory. We believe this applies, in general terms, to information talk in biology. One possibility for building a theory of information in biology is to rely on the mathematical theory of communication. This theory allows one to define the amount of information as the measure of the probability of selection of a particular message among the set of all possible messages. The probabilistic measure of information provided by this theory is nonsemantic, and hence indifferent to meaning (Shannon and Weaver 1949; Cover and Thomas 1999; Jablonka 2002). It is true that this meaning-free concept of information can be useful in biological research for several purposes (Adami 2004). Nevertheless, it has been argued that such a nonsemantic (and quantitative) understanding of information is not sufficient for a theory of biological information, and should be complemented by a semantic, pragmatic (and more qualitative) approach. Jablonka (2002), for instance, uses an example where a DNA sequence encoding a functional enzyme and a same-length sequence coding for a completely nonfunctional polypeptide (which can have only a single different nucleotide) would contain, according to the above-mentioned measure, the same amount of information. It is obvious, however, that these two messages do not mean the

same to the cell. This indicates the necessity of a treatment of information in biology that includes a semantic and a pragmatic dimension. Or, to put it differently, a theory of biological information should also deal with the meaning of messages and the context in which they are interpreted. Here, we use semiotic concepts to build a semantic and pragmatic account of biological information. In particular, we propose a model of information as semiosis, grounded in Peirce's pragmatic theory of signs.

Peircean Semiotics: A Brief Introduction

Peirce is often considered the founder of modern semiotics (Weiss and Burks 1945, 386). Semiotics was defined by Peirce as "the doctrine of the essential and fundamental nature of all varieties of possible semioses" (CP 5:484). Semiotics describes and analyzes the structure of semiotic processes independently of their material bases, or of the conditions under which they can be observed: inside cells (cytosemiosis), among tissues and cell populations (vegetative semiosis), in animal communication (zoosemiosis), or in typically human activities (production of notations, metarepresentations, etc.). In other words, Peirce's concept of semiotics concerns a theory of signs in its most general sense. Peirce conceived general semiotics much like a formal science as mathematics is (CP 2:227). However, semiotics finds the objects of its investigation in the sign's concrete, natural environment and in "normal human experience" (CP 1:241).

Semiotics is subdivided into speculative grammar, critical logic, and speculative rhetoric (CP 2:229). The first division of this science is what interests us here. Its task is that of examining the "sign physiology of all kinds" (CP 2:83), that is, the concrete nature of signs as they emerge and develop, and the conditions that determine the sign's further development, nature, and interpretation. It is the branch that investigates (1) the conditions to which any and every kind of sign must be submitted, (2) the sign itself, and (3) its true nature (CP 1:444). As one of its tasks, speculative grammar elaborates on the classifications of signs or, in other words, the diversity of sign types and how they merge with one another to create complex semiotic processes. For Houser, the logician "who concentrates on speculative grammar investigates representation relations (signs), seeks to work out the necessary and sufficient conditions for representing, and classifies the different possible kinds of representation" (1997, 9). Between 1867 and 1911, Peirce developed a model of signs as processes, actions, and relations, and also elaborated divisions of signs in order to describe different kinds of semiotic processes.

Peirce's pragmatic model of meaning as the "action of signs" (semiosis) has had a deep impact (besides all branches of semiotics) on philosophy, psychology, theoretical biology, and cognitive sciences (see Freeman 1983; Fetzer 1997; Colapietro 1989; Tiercelin 1995; Hoffmeyer 1996; Deacon 1997; Freadman 2004; Hookway 2002). First and foremost, Peirce's semiotics is grounded in a list of categories—namely, Firstness, Secondness, and Thirdness—which corresponds to an exhaustive system of hierarchically organized classes of relations (Houser 1997). This system makes up the formal foundation of Peirce's philosophy (Parker 1998) and his model of semiotic action (Murphey 1993).

In brief, the categories can be defined as follows:

1. Firstness: what something is, without reference to anything else.
2. Secondness: what something is, in relation to something else, but without relation to any third entity.
3. Thirdness: what something is, insofar as it is capable of bringing a second entity into relation to a first one in the same way that it brings itself into relation to the first and the second entities.

Firstness is the category of vagueness and novelty: "firstness is the mode of being which consists in its subject's being positively such as it is regardless of anything else. That can only be a possibility" (CP 1:25). Secondness is the category of reaction, opposition, and differentiation: "generally speaking genuine secondness consists in one thing acting upon another, brute action. . . . I consider the idea of any dyadic relation not involving any third as an idea of secondness" (CP 8:330). Finally, Thirdness is the category of mediation, habit, generality, evolution, and conceptualization (CP 1:340).[5]

Semiosis and Information Processing

According to Peirce (CP 2:171, 2:274), any description of semiosis should necessarily treat it as a relation constituted by three irreducibly connected terms: sign-object-interpretant (S-O-I). Hereafter, we will refer to these terms of a triadic relation as S, O, and I, and to the triadic relation in itself, as "triad" (see figure 4.1). As the reader will note in figure 4.1, this triadic relationship communicates/conveys a form from the object to the interpretant through the sign (symbolized by the horizontal arrow). The other two arrows indicate that the form is conveyed from the object to the interpretant through a determination of the sign by the object, and a determination of the interpretant by the sign.

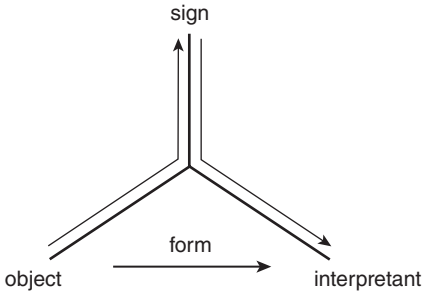

Figure 4.1
The semiotic relationship

For Peirce, a sign is something that stands for something other than itself. Peirce defined signs in several different ways (Marty and Lang 1997), but here we will highlight the definitions that will be useful in our work. He conceived a sign 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). The triadic relation between S, O, and I is regarded by Peirce as irreducible, in the sense that it is not decomposable into any simpler relation. Accordingly, the term "sign" was used by Peirce to designate the irreducible triadic process between S, O, and I, but he also used it to refer to the first term of this triadic relation. Some commentators have proposed that we should distinguish between the "sign in this strict sense" (*representamen*, or sign vehicle), when referring to the first term of the triad, and the "sign in a broad sense" (or sign process, sign as a whole) (e.g., Johansen 1993). Signs, conceived in the broad sense, are never alone.

In Peirce's definitions, we find several clues to understand how signs act. Any sign is something that stands for something else (its object) in such a way that it ends up producing a third relational entity (an interpretant), which is the effect a sign produces on an interpreter. In the context of biosemiotics, an interpreter is a biosystem such as a cell or an organism. In many biological informational processes, sign interpretation results in a new sign within the interpreter, which refers to the same object to which the former sign refers, or ultimately in an action, which can lead to the termination of an informational process. That the interpretant is often another sign, created by the action of a previous sign, is clear in the following statement by Peirce: 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).

Accordingly, it is important to bear in mind always that the interpretant is not necessarily the product of a process that amounts to "interpretation" in the sense that we use this term to account for human cognitive processes. As explained previously, the fundamental character of the interpretant in many biological processes 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, and indeed, refer to it in a similar way.

One of the most remarkable characteristics of Peirce's theory of signs is its commitment to a process philosophy. As a process thinker, it was quite natural that Peirce conceived semiosis as basically a process in which triads are systematically linked to one another so as to form a web (see Gomes et al. 2007). Peirce's theory of signs has a remarkable dynamical nature. According to Merrell, "Peirce's emphasis rests not on content, essence, or substance, but, more properly, on dynamics relations. Events, not things, are highlighted" (1995, 78). Thus, Hausman (1993) refers to the complex S-O-I as the focal factor of a dynamical process.

It is important not to lose sight of the distinction between the interpreter, which is the system that interprets the sign, and the interpretant. The interpreter is described by Peirce as a "Quasi-mind" (CP 4:536), a description that demands, for its proper interpretation, a clear recognition of Peirce's broad concept of mind (Ransdell 1977; Santaella-Braga 1994). It is not the case that only conscious beings can be interpreters in a Peircean framework. Rather, a translation machinery synthesizing proteins from a string of ribonucleic acid (RNA) or a membrane receptor recognizing a given hormone can be regarded as interpreters. A basic idea in a semiotic understanding of living systems is that these systems are interpreters of signs, that is, that they are constantly responding to selected signs in their surroundings. An interpreter is anything that carries on a sign process.

Thus, the interpreter does not have to be a conscious being, not even an organism, as it may be some part or subsystem within an organism, or a human-designed product. Nevertheless, because a sign process is itself an interpreter, the concept of interpreter appears to be secondary in Peirce's semiotics, even though it can play a heuristic role in building some models of semiotic processes.

We also need to consider here Peirce's distinctions regarding the nature of objects and interpretants, (For a review of these topics, see Savan 1988; Liszka 1990; Short 1996.) He distinguishes between the immediate and dynamical objects of a sign as follows:

> We must distinguish between the Immediate Object—i.e., the Object as represented in the sign—and . . . the Dynamical Object, which, from the nature of things, the Sign *cannot* express, which it can only *indicate* and leave the interpreter to find out by *collateral experience*. (CP 8:314; emphasis in the original)

and:

> We have to distinguish the Immediate Object, which is the Object as the Sign itself represents it, and whose Being is thus dependent upon the Representation of it in the Sign, from the Dynamical Object, which is the Reality which by some means contrives to determine the Sign to its Representation. (CP 4:536)

And we should also consider his distinction between three kinds of interpretants:

> The *Immediate Interpretant* is the immediate pertinent possible effect in its unanalyzed primitive entirety. . . . The *Dynamical Interpretant* is the actual effect produced upon a given interpreter on a given occasion in a given stage of his consideration of the Sign. (MS 339d:546–547; emphasis in the original)

and:

> The Final Interpretant is the one Interpretative result to which every Interpreter is destined to come if the Sign is sufficiently considered. . . . The Final Interpretant is that toward which the actual tends. (SS 110–111)

Let us first consider Peirce's distinction between the immediate and the dynamical objects of a sign. The dynamical object is something in reality that determines the sign, but can be represented by the sign only in some of its aspects. These aspects that the sign represents are the immediate object, that is, the dynamical object in its semiotically available form, that is, as immediately given to the sign. In another words, the immediate object is the dynamical object as the sign represents it (this is what we mean by "semiotic availability"). Because the sign represents the dynamical object in some of its features only, never in its totality, it can simply indicate that object, and it is left to an interpreter to establish what is the dynamical object through the interpreter's competence as a user of that sign, which, in turn, results from its previous experience and learning to become an interpreter.[6] This is why Peirce claims that the interpreter should find out what the dynamical object is by collateral experience. The system that is causally affected by the sign should

establish which dynamical object the sign indicates through processes that have been selected for in the evolutionary history of that kind of system. In the ontogenetic timescale, the system will acquire its semiotic competence—that is, its competence as a sign interpreter—through development.

Peirce defines the dynamical interpretant as the actual effect of a sign, while the immediate interpretant is its "range of interpretability"—the range of possible effects that a sign is able to produce (see Johansen 1993, 166–167). The dynamical interpretant is thus the instantiation of one of the possible effects included in the immediate interpretant. The final interpretant in a semiotic process is, in turn, the final state of this process, understood as a tendency being realized when a given chain of triads is triggered, but not determined or bound to happen, because other final states can follow from the semiotic process, as in the case, for instance, of misinterpretation. In one way or another, the final interpretant can be seen as temporally solving the instability that is included into the sign process.

Peirce (CP 8:177) writes that a sign determines an interpretant in some "actual" or "potential" mind (in other passages, a "Quasi-mind"; see CP 4:536). It is indeed possible to differentiate between "potential" and "effective" semiosis. Potential semiosis is defined as a triadically structured process that is not actually taking place, but has a disposition to take place at a given moment; that is, it could occur under the appropriate conditions. Effective semiosis, in turn, concerns a sign that, by being actualized, has an actual effect on the interpreter. Semiosis necessarily entails the instantiation of chains of triadic relations, as 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 triad and the first term (sign) of a subsequent triad (Savan 1988; see figure 4.2). 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 the role of the interpretant in a triad 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.

Please also remember that the outline in this section is purely logical (or semiotic) and that within a particular physical, chemical, or biological system, the semiotic processes described here in general terms can be instantiated by different physical means, such as shifts in chemical con-

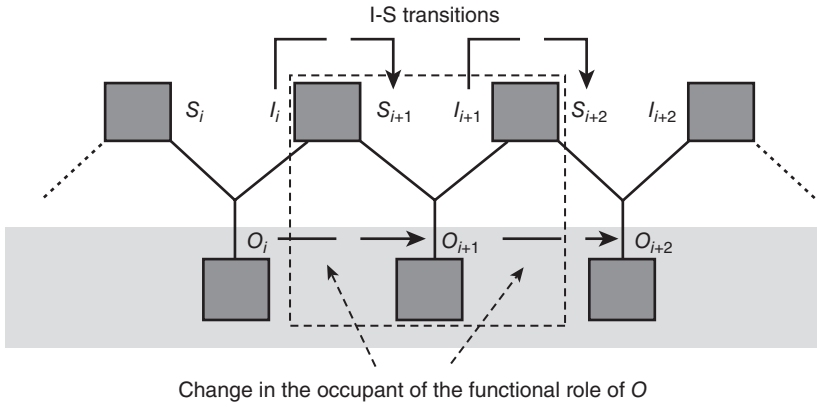

Figure 4.2
The triadic relation S-O-I forms a chain of triads. The grey area at the bottom of the figure shows that all signs in the chain of triads refer to the same dynamical object through a series of immediate objects. The arrows show the interpretant-sign (I-S) transition and the changes in the occupant of the functional role of the immediate object.

centrations or processes of molecular recognition. We will add this material aspect when we present our biosemiotic models.

When the I-S transition takes place, there is also a change in the occupant of the functional role of the immediate object (figure 4.2). 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. Thus, an object turns out to be a plural object via semiosis. We should stress, however, that instead of using the concept of *reference* in these models (as it is a highly debated and sometimes unclear concept that is not included in Peirce's theory of signs), it might be good to replace this concept in future works by a concept internal to Peirce's framework: the concept of *ground*.

As figure 4.2 shows, in a triad *i* 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 in 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 this object through a new immediate object that corresponds to an aspect of the dynamical object represented in the sign. We now have 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 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.

Peirce also defines a sign as a medium for the communication of a form or habit embodied in the object to the interpretant (De Tienne 2003; Hulswit 2001; Bergman 2000), so as to constrain the interpretant as a sign or the interpreter's behavior (figure 4.1):

> A Sign may be defined as a Medium for the communication of a Form. . . . As a medium, the Sign is essentially in a triadic relation, to its Object which determines it, and to its Interpretant which it determines. . . . That which is communicated from the Object through the Sign to the Interpretant is a Form; that is to say, it is nothing like an existent, but is a power, is the fact that something would happen under certain conditions. (MS 793:1–3) (See EP 2:544, n. 22, for a slightly different version.)

What is a form? There is a movement in Peirce's writings from "form as firstness" to "form as thirdness." Form is defined as having the "being of predicate" (EP 2:544), and it is also pragmatically formulated as a "conditional proposition" stating that certain things would happen under specific circumstances (EP 2:388). It is nothing like a thing (De Tienne 2003), but something that is embodied in the object (EP 2:544, n. 22) as a habit, a "rule of action" (CP 5:397), a "disposition" (CP 2:170), a "real potential" (EP 2:388) or, simply, a "permanence of some relation" (CP 1:415). Here, we would like to stress that the form communicated or conveyed from the object to the interpretant through the sign is not the particular shape of an object, or something alike, but a regularity, a habit that allows a given semiotic system to interpret that form as indicative of a particular class of entities, processes, or phenomena, and thus to answer to it in a similarly regular, lawful way. Otherwise, the semiotic system would not be really capable of interpretation.

The communication/conveyance of a form from the object to the interpretant constrains the behavior of an interpreter, in the sense that it brings about a constrained set of relations between the object and the interpretant through the mediation of the sign. We understand the "meaning" of a sign, thus, as an effect of the sign—conceived as a

medium for the communication/conveyance of forms—on an interpreter by means of the triadic relation S-O-I. A meaning process can be thus defined as the action of a sign (semiosis).

In a Peircean approach, information can be strongly associated with the concepts of meaning and semiosis.[7] Peirce spoke of signs as "conveyers," as a "medium" (MS 793), as "embodying meaning." Accordingly, in his theory, the notions of meaning, information, and semiosis intersect and overlap in different ways (see Johansen 1993). Peirce defined "meaning" as the consequence of the triadic relation between sign, object, and interpretant (S-O-I) as a whole (EP 2:429), and also in terms of different correlates of a triad—e.g., object (MS 11, EP 2:274), interpretant (EP 2:496, EP 2:499; CP 4:536; see Fitzgerald 1966, 84; Bergman 2000). In turn, Peirce defined "information" at least ordinarily (CP 2.418) and metaphysically (CP 2.418) as a connection between form and matter, and logically (W 1.276) as the product of the extension and intension of a concept (Debrock 1996).

In the passage quoted earlier from MS 793, Peirce defines a sign both as "a Medium for the communication of a Form" and as "a triadic relation, to its Object which determines it, and to its Interpretant which it determines." If we consider both definitions of a sign, we can say, then, that semiosis is a triadic process of communication/conveyance of a form from the object to the interpretant by the sign mediation. And we can also stipulate that semiosis is, in a Peircean framework, information. For this reason, we systematically refer to *information* as the communication/conveyance of a *form* from O to I through S (Queiroz, Emmeche, and El-Hani. 2005; El-Hani, Queiroz, and Emmeche 2006; Queiroz and El-Hani 2006a, 2006b).

According to our interpretation of Peirce's ideas, information has the nature of a process: it is a process of communicating a form to the interpretant and operates as a constraining influence on possible patterns of interpretative behavior. When applying this general semiotic approach to biological systems, information will most often be an interpreter-dependent process. It cannot be dissociated from the notion of a situated (and actively distributed) communicational agent (potential or effective). It is interpreter-dependent in the sense that information triadically connects representation (sign), object, and an effect (interpretant) on the interpreter (which can be an organism or a part of an organism). In a biological system, information depends on both the interpreter and the object (in which the form communicated in information is embodied as

a constraining factor of the interpretative process). Thus, a framework for thinking about information as a process can be constructed in Peircean terms by employing the following definitions:

- Information = semiosis: a triadic-dependent process through which a form embodied in the object in a regular way is communicated or conveyed to an interpretant through the mediation of a sign.
- Potential information = potential semiosis: a process of communicating or conveying a form from an object to an interpretant through the mediation of a sign that has a disposition to take place at a given moment, changing the state of the interpreter.
- Effective information = effective semiosis: the process by which a sign actually produces an effect (interpretant) on some system (an interpreter) by making the interpretant stand in a similar relation to the same object (the object of the sign) as that in which the sign itself stand. Thus, the sign mediates the relation between object and interpretant. The sign effectively communicates or conveys, in this way, a form from the object to the interpretant, changing the state of the interpreter.

Applied Biosemiotics: Modeling Two Semiotic Processes in Cells

Semiotic Analysis of Genes and Genetic Information

In the genetic information system, the synthesis of proteins and ribonucleic acids (RNAs) is related to deoxyribonucleic acid (DNA). Specific regions of this molecule act as templates for the transcription of RNAs by a multiprotein complex, including RNA polymerase. Messenger RNAs (mRNAs) act, in turn, as templates for the synthesis of proteins in the cytoplasm. DNA can act as a template for the synthesis of RNA, due to the specific base pairing of nucleotides, the monomers that constitute nucleic acids, and RNA in turn can act as a template for the synthesis of proteins due to specific relationships between sequences of three nucleotides (codons) and amino acids, the monomers of proteins. The set of these relationships amounts to the genetic code (which exists in several slightly different versions).

The effects of a protein-coding gene on a given cell or organism are regulated mainly by control of gene expression at the level of transcription initiation. This regulatory process results in the fact that only a subset of all genes present in any cell type in a multicellular organism is actually expressed.

The process by which the nucleotide sequence of mRNA serves as a template for the synthesis of proteins is called *translation* and is an

essential part of protein synthesis. Messenger RNAs are often called the "vehicles" of the genetic information transcribed from DNA. The message at stake is "written" in the form of a series of codons, each specifying a particular amino acid. Another class of RNA molecules, transfer RNAs (tRNAs), play a fundamental role in the process of deciphering the codons in mRNA. Each type of amino acid has its own subset of tRNAs. They act as specific transporters, binding amino acids and carrying them to the growing end of a polypeptide chain in response to specific codons in the mRNA. The reason why the correct tRNA with its attached amino acid is selected at each step in protein synthesis is that each specific tRNA molecule contains a three-nucleotide sequence, called an *anticodon*, which base-pairs with its complementary codon in the mRNA. The specific relationship between tRNAs and amino acids, in turn, results from the attachment of the appropriate amino acid to a tRNA in a reaction catalyzed by a specific aminoacyl-tRNA synthetase. The specificity of the attachment between amino acids and tRNAs results from the capacity of each one of these enzymes to recognize one amino acid and all its compatible, or cognate, tRNAs. Therefore, the rules captured in the genetic code ultimately depend on the recognition activity of aminoacyl-tRNA synthetases.

If we now check the terms presented in the previous paragraphs, we will be able to see "information talk" in action. Our strategy was to use terms that are frequently employed in this same manner in biological papers and textbooks in order to highlight the importance of building a theory to give a precise meaning to this rather metaphorical language. As we mentioned previously, Griffiths (2001) wrote that genetic information is a metaphor in search of a theory. An analysis of molecular biology textbooks (Pitombo, Rocha de Almeida, and El-Hani 2008) shows that this is really so, as no idea related to information other than a reference to sequence information in DNA or proteins is offered in those textbooks as a ground for understanding the "information talk" that pervades them.

Against this background for understanding the genetic information system, we can move on to an analysis of genes and genetic information grounded in Peirce's theory of signs (the original sources for this analysis are Queiroz, Emmeche, and El-Hani. 2005; El-Hani, Queiroz, and Emmeche 2006). From the perspective of this theory, the action of a gene as a sign should be understood as a relationship between three elements (figure 4.3). By employing the definition of "information" put forward previously, genetic information can be thus described as a semiotic

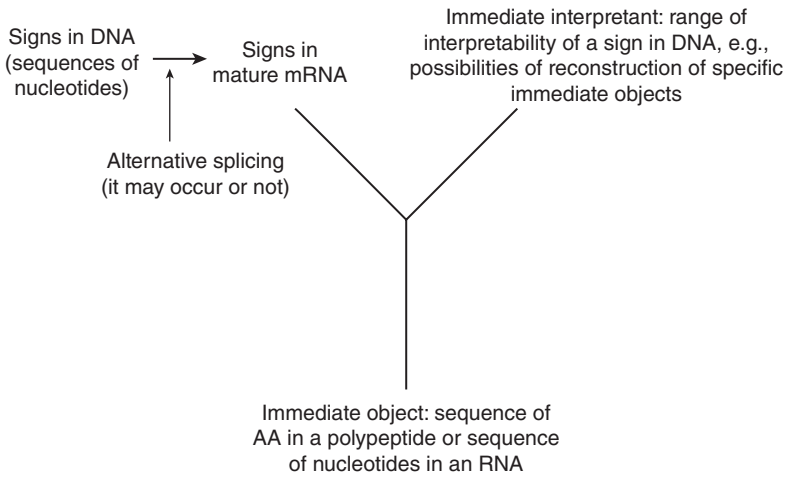

Figure 4.3
A general semiotic analysis of the gene as a sign. A sign is the mediating element in a semiotic process through which a form is communicated from an object to an interpretant. This is the reason why we consider the interpretant here as the reconstruction of a form (habit) embodied in an object. "Reconstruction" here amounts to a process by which the form of a protein in a cell generation is communicated through signs in DNA (in potency) to the form of a protein in the next cell generation. Thus, a regularity obtains in the three-dimensional structure and function of proteins over generations.

process. From this perspective, there is more to genetic information than just the sequence of nucleotides in a stretch of DNA. This is an important conclusion, as it goes against the treatment of genetic information as merely sequence information in DNA or proteins, and indicates a different path to conceptualize information, that is, in a theory of biological information grounded in Peircean semiotics.

In figure 4.3, a sequence of nucleotides in DNA is not treated as information in itself, but as the first correlate of information interpreted as semiosis—that is, a sign. Signs in DNA are transcribed into signs in mature mRNA, with or without the occurrence of alternative splicing, a process through which different patterns of RNA processing lead to a number of different mature RNA molecules, each coding for different, but related proteins (isoforms). If alternative splicing takes place, a sign in DNA will then be used to produce several different signs in mRNA. The immediate object of a gene as a sign in DNA is the sequence of amino acids or nucleotides represented in it. And as several different immediate objects can be represented in DNA (given processes such as

alternative splicing), there is a range of interpretability of a sign in DNA, which amounts to the immediate interpretant.

A protein-coding gene, for instance, can become a sign in effective action in a cell only by standing—in a triadic-dependent relation—for a specific sequence of amino acids (immediate object) through a process of reconstruction of a specific form (interpretant). What is genetic information in this scheme? It can be understood as the whole process through which a gene acts as a sign in a given cell, mediating the reconstruction of a specific sequence of amino acids. Information is the triadic-dependent relation per se; it is a process, not something to be found in the first correlate of this process, a sign in DNA. In signs in DNA, we can find information only *in potency*. When this potential information becomes actual information, it is not something contained in isolated signs in DNA, but the very process through which those signs act.

The relationship between signs in DNA and sequences of amino acids in proteins is established by a complex mechanism of interpretation, involving transcription, RNA processing, and translation.[8] Thus, to interpret a string of DNA, more than one interpretative system is required, including, for instance, RNA polymerases, involved in the transcription of DNA into RNA, and ribosomes, involved in the translation of mRNA, into protein. These interpretative systems are parts or subsystems of a cell as a global interpreter, and their actions are subordinated to the latter. The idea that the cell can be seen as a global interpreter to which a series of interpretative subsystems in the genetic information system are subordinated is dramatically reinforced by recent analyses of the functional organization of proteomes. Consider, for instance, that the multicomponent cellular systems involved in transcription, RNA processing, and RNA transport do not form a simple linear assembly line, but a complex and extensively coupled network in which signals circulate in a nonlinear manner, involving several feedback loops (Maniatis and Reed 2002; Kornblihtt et al. 2004). It is this network structure that makes possible the coordination of the interpretative subsystems in the genetic information system by the cell.

It is clear, then, that we cannot easily move from claims at the cellular level to claims at the molecular level while pondering which system is interpreting genes as signs. It is becoming increasingly clear through recent advances in the understanding of cell systems that when a gene is interpreted, the interpretation process is indeed taking place at the cellular level, although multicomponent molecular subsystems are necessary

to this endeavor. This idea that ultimately the whole cell participates in the network necessary for the interpretation that is demanded for the effect of a gene product to take place (Emmeche and Hoffmeyer 1991; Pardini and Guimarães 1992) is further supported by the role of an impressive array of signaling pathways regulating the interpretation of signs in DNA. As Fogle observes, "DNA action and function become meaningful in the context of a cellular system. Coding information in the DNA is necessary but insufficient for the operation of living systems" (2000, 19).

Accordingly, a Peircean approach to genes and genetic information entails that genetic structures should not be seen in isolation from the larger system by which they are interpreted. From this perspective, the meaning of a gene to its interpreter, the cell—or, to put it differently, the biological meaningfulness of a gene—is found not only in DNA sequences in a chromosome. That there is more to genetic information than just a sequence of nucleotides in DNA means that we will have to include in our models of information the effect of the gene-as-a-sign on the cell or organism, and, in fact, the very role of cellular subsystems as interpreters of strings of DNA, in such a way that they relate signs to specific dynamical objects, proteins that play a function inside the cellular system and have an effect on it or on the organism of which the cell is a part.

In a Peircean framework, we move from an identification of genetic information with sequential information in DNA to its understanding as a triadic-dependent, semiotic process. As a way of stressing the difference between an account of information as a process and more usual explanations about what is information, consider, for instance, Maynard Smith and Szathmáry's (1999, 9–10) argument that information is "that something" that is conserved throughout a series of changes in the material medium underlying a communication process. According to the model developed previously, "that conserved something" is not information, but rather the permanence of a certain relation in the reconstructed form. Information is rather the process by which a form is conveyed through several different media (signs) in such a way that a relational structure is conserved throughout the process, even though the significant aspects of the object's form are continually reconstructed. Applying this idea in the context of the analysis offered in this section, it is not genetic information that is conserved throughout the different tokens of DNA molecules (different material media) in different organisms and generations, but rather a relational structure in the reconstructed form, that is, a habit

or a tendency to build tokens of the same kind of protein (in the case of a protein-coding gene) based on the signs available in DNA. These signs themselves can only harbor potential information. Genetic information, in turn, is taken to be the process by which the permanence of a relational structure is conveyed to a new token of a protein, that is, the whole process through which genes as signs in DNA (entailing the potentiality of genetic information as a process) are irreducibly related to objects and interpretants.

Even if one concedes that this argument shows an advantage of our account in relation to the one given by Maynard Smith and Szathmáry, there is a further issue to be considered. Both accounts must meet the important requirement of providing an explanation of the representational character of signs. Prior to its application to biological processes, one might get the impression that the Peircean model of semiosis as a triadic relationship is simply a formal, uninterpreted schema. How, then, when applied to biological phenomena, does the representative character of a sign take on a specific meaning? On Maynard Smith's (2000) view, the representational nature of signs is explained by bringing in the idea of formal and/or final causation. We are also sympathetic with these causal notions. Therefore, despite the difference pointed out earlier, there are also similarities between our account and Maynard Smith's with regard to the explanation of the representational character of a sign in the biological sphere. However, a crucial advantage of the Peircean model is that what superficially looks like simply a formal definition of the logic structure of the sign is in fact also a pragmatic definition of the structure of meaning, because the meaning of a sign can be accessed only through that sign's effect (interpretant) upon some interpreting system, such as a cell or an organism. Thus, if we offer an answer, for specific biological cases, to the problem of how a sign takes on a specific meaning, this does not mean that we should be committed to look for any mysterious additional emergence of the representative character of the sign. The origin of semantic-pragmatic meaning is embedded within the same triadic formal structure of the sign interpretation process, that is, as the process by which new interpretants are generated.[9]

Transcription, RNA processing, and protein synthesis can be understood, in semiotic terms, as processes of actualization of potential signs in protein-coding genes. When put into action, a protein-coding gene becomes part of effective semiosis, a triadic-dependent process by means of which the gene as a sign indicates a given functional product, synthesized after splicing, mRNA edition, or any other complexity involved in

the path from a DNA stretch to a protein. This functional product has, in turn, an effect on the organism in which it is expressed (its final interpretant), participating in its adaptive interactions with its surroundings, and thus contributing to the presence of those potential signs in the next generation in a high frequency. Notice that we are not postulating any inversion of the central dogma (as if sequences of amino acids in proteins might determine sequences of nucleotides in DNA). We are referring, rather, to the effect of functional proteins on the likelihood that certain genes—certain signs mediating the process of the synthesis of those proteins—will be present in future generations.

The actualization of a gene depends on boundary conditions established by a higher-level semiotic network, a network of signaling processes that regulate gene expression, ultimately determining the likelihood of transcription of a given gene, or splicing of a given pre-mRNA according to a particular pattern, or chemical modification of a given protein in a manner that modulates its function in a particular way (e.g., by phosphorylation), and so on. A variety of regulatory mechanisms studied in cellular and molecular biology can be thus understood as composing a macrosemiotic environment, establishing boundary conditions that will downwardly determine which potential genes in a string of DNA will be actualized, entering into effective action in a cell.

This shows how several complexities involved in gene expression can be introduced in our analysis: boundary conditions established by this macrosemiotic environment will determine, for instance, which stretch of DNA will be read (e.g., allowing for an analysis of transcription of overlapped or nested genes), which pattern of RNA splicing or RNA editing will be instantiated in order to produce a particular mature mRNA (allowing for the subtleties of alternative RNA splicing or RNA editing to be taken into account), which functional protein will be effectively constructed by the cell (allowing for chemical and/or structural modifications suffered by the primary amino acid sequence of a protein to be considered), and so on.

The regulatory influence of the macrosemiotic level—that is, of the network of signaling processes on interpretative subsystems, and, thus, on transcription, splicing, translation—shows that we have to ultimately consider the whole cell as participating in the network necessary for the actualization of potential genes in DNA. The cellular network of semiotic processes is, in turn, highly responsive to environmental factors, given the semi-open nature of living systems. Accordingly, genes, as potential signs in DNA, are actualized in response to regulatory dispositions

arising from a network of signaling pathways that elicit cellular specific responses to other signs arising from a hierarchy of contexts, environments, or, in our own terms, semiotic levels that can direct gene expression (i.e., establish boundary conditions for the selection of potential genes in DNA), ranging from systems of gene-gene interactions to organisms, and passing through nucleus, cytoplasm, cell, cell surface, extracellular matrix, morphogenetic fields, collective condensations of cells (blastemas), organs, and so on (see, for example, Hall, 2001). Thus, the cell, as an interpreter, answers to an environmental cue or sign by means of a specific alteration of its internal states, triggered by a whole network of signal transduction culminating in a change at some level of gene regulation. (A semiotic analysis of signal transduction systems follows. See also Bruni 2003, Queiroz and El-Hani 2006b, and El-Hani, Arnellos, and Queiroz 2007.) These relations cannot be understood only in terms of molecular interactions taking place in networks of signal transduction, because this latter process crucially involves semiotic events, as the widespread usage of information talk in modeling and explaining signaling pathways clearly suggests.

This semiotic analysis also allows us to offer an interesting account of the "transmission" of information. It is not effective information that is being communicated when one observes, for instance, "vertical transmission" from parent to offspring. From the perspective of the model explained earlier, what is being communicated is only potential information, that is, the potentiality of a process called "information." It is only this potentiality that can be said, as explained prior, to be carried by stretches of DNA. Signs in DNA will become elements in effective information only when interpreted by the cell. Effective information itself cannot be carried from one system to another; only potential information can be carried by the first correlates of triads, signs (which, in biological systems, are typically physicochemical entities).

This biosemiotic analysis of the genetic information system leads to the following conclusions:

1. Genes should be treated as signs in DNA, which can have an effect on a cell only through a triadic-dependent process (semiosis).
2. This process *is* genetic information and involves more than just genes as signs in DNA but also objects and interpretants.
3. Genetic information is the process by means of which a form in a dynamical object (a functional protein) is communicated to an interpretant (the reconstruction of a specific sequence of amino acids in a cell) through signs in DNA.

Let us now turn to the semiotic modeling of signaling systems to which we referred earlier when discussing the macrosemiotic environment within which genes, as potential signs in DNA, are downwardly selected to be actualized.

A Semiotic Model of Signal Transduction in B Cell Activation

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 and Wienands 1997). BCR has two functions in B cell activation (Pierce 2002): it initiates signaling pathways that result in a series of intracellular processes 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.

Reth and Wienands (1997) proposed a model of molecular interactions in signaling pathways based on functional definitions, intended to express the roles played by several elements in such pathways, acknowledging (as it is proper of functional definitions) that different elements can fulfill those roles, or, to put it differently, be the occupants of the functional roles described in the model in different signaling processes. Such a functional model has the important characteristic of being general, in contrast to molecular, mechanistic models of particular signaling pathways. Reth and Wienands characterize eight functional categories of signaling elements (figure 4.4).

Through signal transduction, living systems are capable of internalizing a cue to a certain aspect of the environment, by producing intracellular signs in response to an extracellular sign. *Receptors* play a central role in the processes through which a cell shows the capacity of answering to its surroundings. A receptor is in most cases a transmembrane protein that undergoes, when bound by an extracellular ligand, a conformational or topological (e.g., receptor aggregation) change that is, according to Reth and Wienands, "transmitted into the cell" (1997, 456). But how is the molecular change suffered by the receptor communicated to the intracellular milieu? Here, *transducers* enter into action. (But the issue of how the reference to the same cue or signal is maintained in the several changes in the material basis of the message remains open, and is indeed the matter to be dealt with in semiotic models.) Receptors

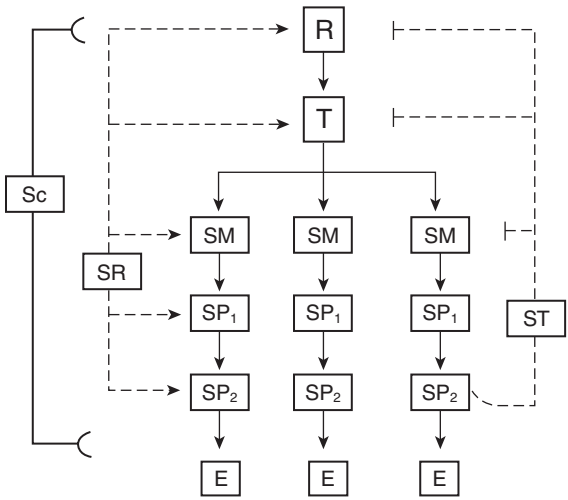

Figure 4.4
Reth and Wienands's (1997) functional model of signaling pathways. Arrows represent different types of functional connections between signaling elements. Dashed arrows represent regulatory relationships: R, receptor; T, transducer; SM, signal manager; SP, signal processor; SR, signal regulator; ST, signal terminator; Sc, scaffold protein; E, effector.

usually do not have an intracellular catalytic domain and are thus dependent on transducer elements to carry out their signaling function. In most cases, transducers are enzymes physically associated with the intracellular part of the receptor. In its resting state, the receptor often represses signaling activity of the associated transducer, but when it is activated by ligand binding, it suffers a conformational or topological change that leads to the activation of the transducer.

Each signaling pathway is switched on by the activity of the transducer and controlled by a *signal manager*, the third category in Reth and Wienands' (1997) model, located at the start of a particular signaling route. There can be several signaling pathways arising from the same receptor. There are cases in which a signal manager interacts directly with an effector, which instantiates an action under the regulation of the signaling pathway. When this is not the case, the signal manager activates a signal cascade consisting of one or several *signal processors*. *Signal regulators*, in turn, modify the efficiency and duration of signals traveling down a signaling pathway, by amplifying or decreasing the signal. Such changes in the intensity of a signal can have major biological effects. As we can see in figure 4.4, signal regulators can act at the level of receptors,

transducers, signal managers or signal processors, that is, at all functional levels of the signaling system.

Signal transduction occurs in an organized microenvironment, in which different elements of a signaling pathway are connected both functionally and spatially. This architecture of signaling elements can be established before or after the activation of a receptor. In the former case, *scaffold* or *adaptor proteins* play an important role in organizing the spatial and functional architecture of signaling elements, by bringing them together in a preformed protein complex.

Even if the stimulus is persistent, signal transduction through many receptors is terminated after some time, due to the activity of *signal terminators*, which can be phosphatases as well as kinases or GTPases. They establish a feedback loop that changes the activity of the receptor, transducer, and/or a particular signal manager. At the endpoint of a signaling pathway, one finds one or several *effectors*, which can be enzymes, transcription factors, or cytoskeletal elements. They are the elements whose behavior is modulated by the signaling pathway.

We stated previously that signal transduction is a process through which living systems can answer in a regular and (usually but not always) adaptive manner to the environment, by producing intracellular signs in response to extracellular signs. The mechanistic interactions involved in this process are aptly modeled by Reth and Wienands in functional (and, thus, properly general) terms, but, if the series of mechanistic interactions that take place in a signaling pathway amounts to a process of *signal transduction*, a description in terms of molecular interactions or even functional definitions will not be enough. It is not that some additional element, besides the molecules themselves, should be added to the mechanistic and material aspect of the signaling pathway; rather, what should be added to the picture is the kind of relation explained earlier, a semiotic relation by means of which a molecule such as an antigen can be a sign that stands for something else—say, a pathogen—and, in turn, lead to the production, within the living system, of other (signaling) molecules that 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 and functional roles in a pathway, but also the maintenance of the reference to the same object, namely the pathogen, while several different signaling molecules are engaged in the pathway. This is clearly a fundamental property to account for, if we want to explain why this is a signal transduction process.

In more detail, to model in Peircean terms the maintenance of the reference to an extracellular sign throughout the several changes in intracellular signs that characterize a signaling pathway, one should consider how the processes described by Reth and Wienands instantiate a triadic relation in which a receptor that acts as an interpreting system recognizes a sign (the extracellular signal, an antigen), which refers to an object in the world (a dynamical object, such as a pathogen) through a feature semiotically available in its representation (the molecular form of the antigen, as an immediate object that indicates the pathogen, as a dynamical object). Receptors act as interpreting systems by activating transducers in response to ligands (signs). That is, the receptor communicates the sign process to the interior by coupling to transducers, catalytic molecules that trigger the production of another sign inside the cell in response to the extracellular sign. This subsequent sign is the interpretant of a first triadic relation, and it takes the role of a sign for a subsequent triadic relation, allowing signaling to proceed. This happens through a series of intracellular signs that can diverge, if several signaling pathways are triggered by the transduction of a single extracellular sign, and are amplified by signal regulators along the pathways. Each pathway ends in an effector, which produces the final interpretant in the process, an action through which sign interpretation has an effect on the cell phenotype.

Let us take now a closer look at initiation events at the BCR signaling system. Figure 4.5 presents a model of the main events at stake. In resting B cells, BCR is excluded from membrane domains (lipid rafts) that 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 those domains. Stable residency in lipid rafts results in association with *Lyn*, which phosphorylates BCR, initiating several signaling pathways. In figure 4.5, another kinase is shown, named *Syk*, which initiates one of the signaling pathways resulting from BCR activation.

As we saw earlier, when interpreted from a Peircean perspective, an antigen is a sign that stands for something else, such as a pathogen, and a receptor such as BCR acts as an interpreting system in the cell membrane, triggering processes by means of which new signs—that is, interpretants—are produced inside the B cell. The first interpretant in this case is the phosphorylated state of BCR, which is a sign that stands for the pathogen as the antigen itself stood for it. This generates a new triad, linked to the previous one by the double role played by the

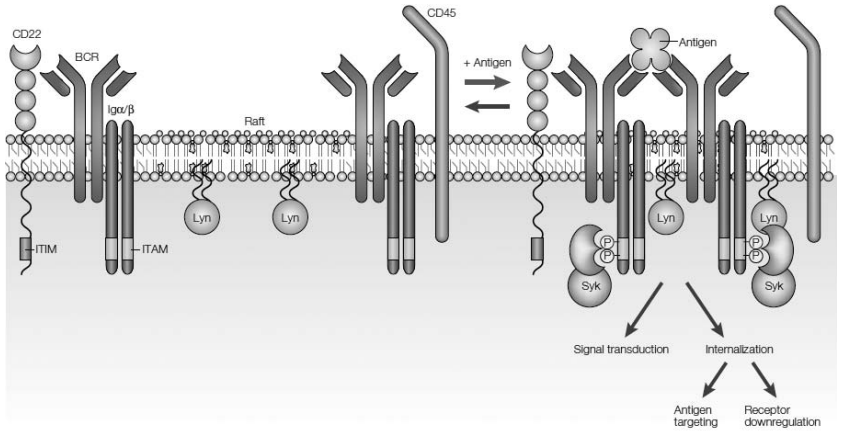

Figure 4.5
Model of the initiating events in the signal-transduction pathways leading to B cell activation (from Pierce 2002)

phosphorylated state of BCR, which is both the interpretant of a first triad, and the sign of a second triad (figure 4.6). We are dealing, thus, 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 pathogen which was represented in the antigen (O_i) is now 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 4.6).

It is this latter change that makes it possible for the same entity or process to be kept as a stable referent throughout the signaling process, despite the several changes in the material bases of signaling, that is, in the signs involved. The maintenance of the reference to the pathogen in a signaling pathway can be modeled as such changes of occupants because all the immediate objects in a chain of triads stand for the same dynamical object—the pathogen. The fact that the reference to the same dynamical object is maintained can be explained on the basis that the latter is, in a Peircean framework, the primary constraining factor in semiosis, because its form—understood as a regularity or habit—is communicated through several semiotic, triadic relations. Such a communication of the form of the dynamical object, as semiotically available in a series of immediate objects, is *information* in a signaling pathway. After all, information is conceived, in the Peircean framework developed here, as a triadic-dependent process through which a form embodied in the

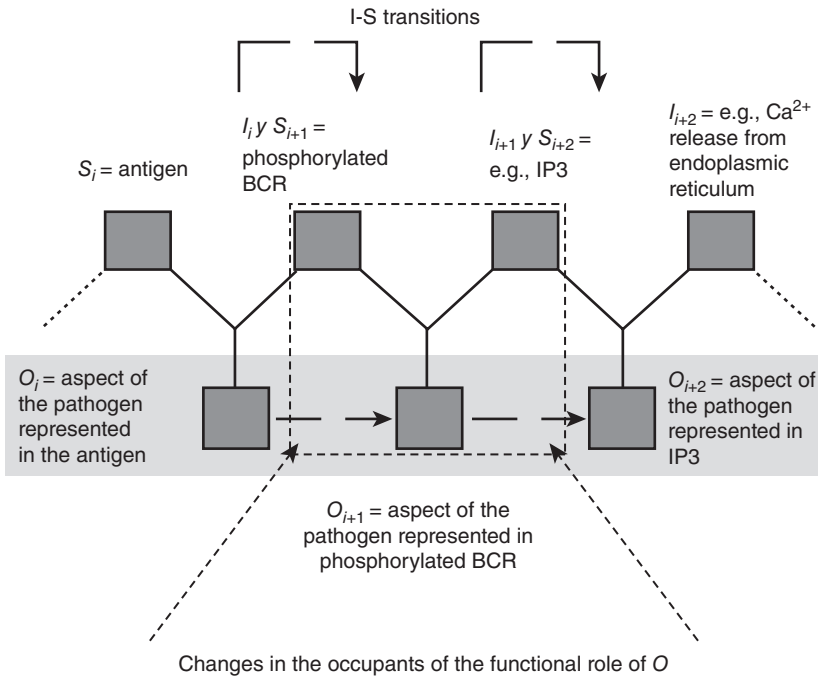

Figure 4.6
A model of one of the signaling pathways triggered by activated BCR as a chain of triads. Notice the I-S transition and the changes in the occupants of the functional role of O. The maintenance of the reference to the pathogen in a signaling pathway is modeled in terms of these changes of occupants, because all the immediate objects stand for the same dynamical object, the pathogen, throughout semiotic, triadic relations that communicates the form of the object and are conceived, according to the theoretical framework developed here, as *information* in a signaling pathway.

object in a regular way is communicated to an interpretant through the mediation of a sign.

Biochemical and genetic evidence has shown that *Syk* has a key role in a well-defined pathway of B cell activation, which results in 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 a new interpretant in 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 in cell metabolism, and also in signaling, make it clear how an original sign-response can be broadly diversified by the signaling systems of a cell. As we can see in figure 4.7, the pathway managed by *Syk* in which IP3 is involved does not end in Ca^{2+} ions, but continues through further I-S transitions, which we will not model here for reasons of space. The final interpretant of this (and other) signaling process amounts to the regulation of gene expression so as to lead to B cell activation.

DAG and IP3 stand for the pathogen in the same way as the antigen and the phosphorylated state of BCR stood, maintaining the reference

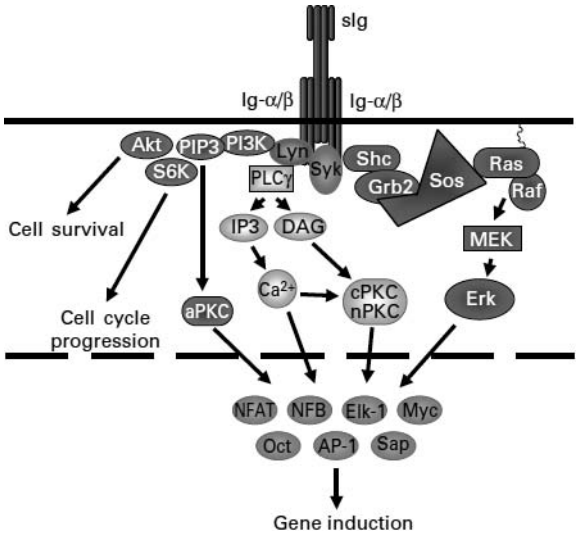

Figure 4.7
Several intracellular signaling pathways are initiated by the cross-linking of B cell receptors by antigen (Goodridge and Harnett 2005). In the center of the figure, one can see the signaling pathways modeled above, involving *Syk*, *PLCγ*, IP3, and Ca^{2+} release. Notice the integration between this signaling pathway and the one involving DAG, which leads to the activation of *cPKC* and *nPKC*. Notice, also, that the pathway involving IP3 and Ca^{2+} regulates in the end patterns of gene expression in B cells.

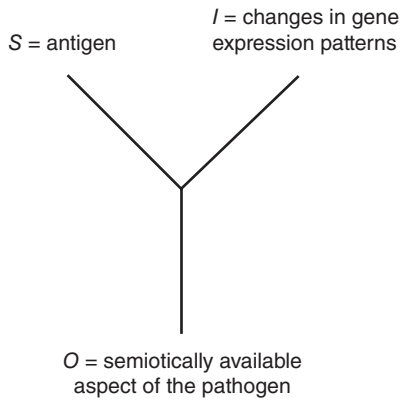

Figure 4.8
A global semiotic analysis of a semiotic process triggered by antigen-binding to BCR

of the signaling process through changes of the occupants of the functional role of the immediate object. IP3, for instance, acts as a sign to a subsequent triad, triggering the production of Ca^{2+}, which in turn will occupy the role of sign in a further triad, up to the final interpretant of this particular semiotic process.

From a global perspective, the overall result of the semiotic process modeled previously can be grasped in terms of a triad containing the antigen as a sign, the pathogen as represented, say, in the three-dimensional form of the antigen as an immediate object, and changes in the pattern of gene expression in B cells, as an interpretant (figure 4.8).

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 pathogen—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, triadic model capable of showing how the reference to a non-self entity external to the cell can be maintained during the processing of signs 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 of 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 pathogen is maintained, while the material bases of the message—namely, the signs—keep changing throughout the process.

To put it differently, we argue that to understand signaling processes, we need at least three properly connected, but different models:

1. Molecular, mechanistic models of particular signaling pathways, in which the molecular interactions that take place in them are properly represented and explained
2. General, functional models, such as the one proposed by Reth and Wienands (1997), which represent and explain in general terms how different occupants can play the several functional roles in a signaling pathway
3. Semiotic models, such as the one proposed by El-Hani, Arnellos, and Queiroz (2007), and reviewed and extended here, which represent and explain in semiotic terms how different occupants can play the same semiotic roles in a signaling pathway

Finally, consider the role of signaling processes, as a higher-level semiotic network, in the actualization of genes as potential signs, by affecting the likelihood of their transcription, or the patterns of splicing of their pre-mRNA, or posttranslational changes of their functional products. Accordingly, the next step in our research will be to employ the basic framework developed herein to model signal transduction in connection with gene actualization, combining in a single model the accounts we developed in separate papers.

Concluding Remarks

The framework for building a theory of biological information presented here is consistent with the general picture of genetic information and signaling processes in genetics and molecular biology, with the fundamental differences that first, a concept of information is explicitly formulated within a heuristically powerful theoretical framework, and second, information is on these grounds conceptualized as a process. Consequently, to make this semiotic framework and the current structure of genetics and molecular biology compatible, it is necessary to conceive the latter in more process-oriented terms. This is a fruitful avenue to be

pursued in order to build a framework for biology that is more compatible with the increasingly complex and dynamic nature of biological systems revealed by recent advances in the biological sciences (for some suggestions to the same effect, see, e.g., Neumann-Held 2001; Keller 2005). We consider the compatibility of our semiotic analyses with the framework of genetics and molecular biology as a strong feature. Of course, the pros and cons of complementing the current models in genetics and molecular biology with a semiotic concept of information is a matter for further investigation.

We have argued that semiotic modeling is a necessary counterpart to functional and mechanistic models of genetic and signaling systems. The conceptual tools offered by Peircean semiotics, along with the biosemiotic models that they enable us to construct, can deepen our understanding of biological phenomena that are described by a communicational and informational vocabulary. This is particularly important in a time in which biology is increasingly seen as a science of information. It is always useful to remind ourselves that at present we do not have an established general notion of biological information (despite the roles that the meaning-free concept of information offered by the mathematical theory of communication can play in biological research), and it is a basic contention of this work that biosemiotics can help in building a semantic/pragmatic concept of biological information.

Notes

1. In the body of the chapter, Peirce's works will be referred to as CP (followed by volume and paragraph number) for quotations from the *Collected Papers of Charles Sanders Peirce, 1866–1913* (Peirce 1932–1935); EP (followed by volume and page number) for quotations from *The essential Peirce: Selected philosophical writings, 1893–1913* (Peirce 1998); MS (followed by the number of the manuscript) for quotations from *The Annotated Catalogue of the Papers of Charles S. Peirce* (Peirce 1967); and SS (followed by page number) for quotations from *Semiotic and Significs: The Correspondence between Charles S. Peirce and Victoria Lady Welby* (Peirce 1977).

2. A review of the history of biosemiotics can be found in Favareau 2007 and Kull 1999. See also Emmeche, Kull, and Stjernfelt 2002.

3. In the Peircean framework, the interpretant is the effect produced by a sign. The concept will be explained in more detail later in this chapter in "Semiosis and Information Processing."

4. If one prefers not to use the category of causality to explain these aspects of living systems, one may speak of formal and final *determination*, in a framework

that acknowledges the existence of other kinds of determination in natural systems, besides causal determination (see El-Hani and Queiroz 2005).

5. For further discussion of the categories, see Hookway 1985, Murphey 1993, and Potter 1967/1997.

6. By "learning" here, we mean the result of both ontogenetic and phylogenetic processes that can lead a system to improve its sign-interpreter abilities.

7. Also, with the concept of experience (CP 1:537).

8. A detailed semiotic model of transcription and translation is put forward by El-Hani, Queiroz, and Emmeche (2006).

9. Much more could be said about Maynard Smith's views about biological information and the concept of representation, generally speaking, but this would require more space than we can devote to this issue in the framework of the current chapter.

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