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LETTER TO THE EDITOR

From Biosemiotics to Code Biology

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This letter is an account of the reasons why I joined the biosemiotic movement in 2001, became the founder and editor-in-chief of the journal *Biosemiotics*, and resigned from that position in 2012 in order to develop the new research field of Code Biology. It is a twelve-year-long story that revolved around the issue of *meaning* in Nature: "Is meaning a natural entity?" or, in a slightly different form, "Can we introduce meaning in biology?" In 2001, it seemed to me that biosemiotics had the potential to tackle this problem and that is why I joined in. I was aware that most biosemioticians were critical of the scientific method, but I was confident that, in due course, reason would prevail. Twelve years later I realized that I had been wrong. Biosemiotics could not be reconciled with science, and the only way to introduce meaning in biology was the new approach that became known as Code Biology. This, in a nutshell, is the message of this letter. It is a personal account, of course, but science is made by individuals, and what I am trying to do here is to recount what happened as best as I can.

The story started in 2001, when Thomas Sebeok, as editor-in-chief of *Semiotica*, asked me to review a special issue of that journal entitled "Jakob von Uexküll: A Paradigm for Biology and Semiotics." It was a massive, 828-page-long volume, written by 41 academics from 15 different countries, with papers on history, philosophy, theoretical biology, ecology, linguistics, arts, literature, and computer science, all dedicated to celebrating Uexküll as a precursor and architect of biosemiotics. That celebration was very dear to Sebeok, because it was the crowning of his lifelong project to put semiotics—the study of signs—on a firm biological basis. Sebeok realized this project first by developing the field of *zoosemiotics*, and then by extending it into the larger field of *biosemiotics*.

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Zoosemiotics

The idea that animals have feelings, moods, and even minds has been entertained in various ways throughout the centuries, but for a long time it has been taken almost for granted that only humans are capable of *semiosis*, i.e., the use of *signs*. This idea was explicitly challenged for the first time in 1963, when Sebeok suggested that animal communication is also based on signs and proposed the term *zoosemiotics* for the new science of *animal semiosis* (Sebeok 1963, 1972).

This proposal set Sebeok on a long search for evidence of semiosis in various fields of the life sciences, and eventually the hunt paid off. In the last account of his long chase, Sebeok (2001) declared that he got the crucial clue from biologist Jakob von Uexküll (1864–1944) by reading, in 1976, the original German edition of *Theoretische Biologie* (von Uexküll 1928).

The great insight of this book is that animals can play, cheat, threaten, court, and act, all of which suggests that they are *interpreting* what goes on around them, and not just reacting automatically as preprogrammed puppets. But is the ability to interpret the world enough to prove that animals are capable of semiosis? The answer depends of course on what we mean by semiosis, and on this point there were, in the 1960s, two major schools of thought: one founded by the Swiss linguist de Saussure (1916), the other by the American philosopher Peirce (1906).

The main difference between the two schools is that Saussure defined the sign as a dual entity, a combination of

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signifier and *signified*, whereas Peirce insisted that it is a triadic relationship between a *sign vehicle*, an *object*, and an *interpretant*. According to Peirce, any act of signification, i.e., any *semiosis*, is necessarily a process of *interpretation*, and this is the view that Sebeok, a pupil of Charles Morris, came to regard as the true definition of semiosis.

The combination of Uexküll's evidence that animals are "interpreters" with Peirce's concept that "interpretation" is the hallmark of semiosis allowed Sebeok to conclude that animals are indeed semiotic creatures. Sebeok, furthermore, was able to account for the differences that exist between human and animal semiosis by pointing to the existence of three different types of signs that Peirce (1906) had called *icons*, *indexes*, and *symbols*.

(1) Icons are signs that represent objects in virtue of a *similarity* that exists between them, and similarities are useful because they allow animals to recognize objects from a few general features.
(2) Indexes are signs that represent objects because of a *physical link* between them. Footprints, for example, are signs of preceding animals, smoke is a sign of fire, and so on. Indexes are the basic tools of learning because they allow animals to infer the existence of something from a few physical traces of something else.
(3) Symbols are signs that represent objects in virtue of entirely *arbitrary* links that are established between them. There is no similarity and no physical link between a family name and a person, for example, or between a flag and a country. Symbols allow us to make arbitrary associations and build mental images of hypothetical events (projects), of abstract things (numbers), and even of nonexistent things (unicorns).

It is an experimental fact that human culture, and language in particular, is massively dependent on symbols, whereas animal communication is based almost exclusively on icons and indexes. It is true that some examples of symbolic activity have been reported in animals, but in no way can they be regarded as primitive languages or intermediate stages toward language. A pervasive and systematic use of symbols is indeed uniquely human, but icons and indexes too are signs, and this is what allowed Sebeok to conclude that animal semiosis is a reality.

Biosemiotics

After the pioneering work of Jacob von Uexküll, the study of animal behavior has grown into a research field in its own right, and has proved with countless examples that animals are indeed interpreters, in species-specific ways, of what goes on in the world around them. In the Peircean framework, on the other hand, interpretation is the defining feature of semioisis, and this allowed Sebeok to conclude that semiosis exists in all animals and not only in humans. But why should semiosis be confined to animals? What about other living creatures? By the 1980s, there were at least three lines of evidence that suggested the presence of semiosis beyond the animal kingdom.

(1) Florkin (1974) argued that the genetic code is proof that semiosis exists at the molecular level and its study represents a new field of research, to which he gave the name of *molecular biosemiotics*.
(2) Krampen (1981) pointed out that plants too make use of signs, and engage in a plant-specific type of communication that he called *phytosemiosis*.
(3) Free-living single cells make up the great majority of the living world, and countless studies have shown that their behavior is *context-dependent*, in the sense that they can react in different ways to different environmental conditions. In this respect they appear to be similar to animals, and that suggested that the context-dependent behavior of microorganisms is evidence that they have the ability to interpret the signals from the environment.

This is why Sebeok in 1983 proposed to a group of colleagues to investigate the possibility that Peirce's semiotics could become a paradigm for the whole of biology. The result of that teamwork was published the following year with the title, "A Semiotic Perspective on the Sciences: Steps toward a New Paradigm" (Anderson et al. 1984), and became the "manifesto" of a synthesis between biology and semiotics that shortly afterwards was referred to as *biosemiotics*.

A few years later Sebeok organized a series of international meetings at Glottertal, near Freiburg, and it was in one of those meetings, in 1990, that Sebeok met Jesper Hoffmeyer, a Danish biochemist who had founded a Society for the Semiotics of Nature in Copenhagen. Shortly afterwards, in 1992, came the encounter with Kalevi Kull, who was organizing the Jakob von Uexküll Center in Tartu, Estonia.

Hoffmeyer and Kull were biologists, not semioticians, and their joining in turned biosemiotics into a fully interdisciplinary enterprise. It also marked the transition to a younger generation, and perhaps it is fair to say that the passing of the testimonial from Sebeok to Hoffmeyer took place in 2001, when the first Gathering in Biosemiotics was organized by Hoffmeyer in Copenhagen (Kull 2001; Favareau 2007).

The formal definition of semiosis in terms of interpretation appeared in the treatise edited by Posner et al. in 1997, and was expressed in these terms: "*The necessary and sufficient condition for something to be a semiosis is* *that A interprets B as representing C, where A is the interpretant, B is an object and C is the meaning that A assigns to B*" (Posner et al. 1997, p. 4; italics added).

As a result of Sebeok's influence, it has been taken almost for granted in biosemiotics that interpretation is the defining feature of both semiosis and life. Sebeok expressed this concept with utmost clarity: *"Because there can be no semiosis without interpretability—surely life's cardinal propensity—semiosis presupposes the axiomatic identity of the semiosphere with the biosphere"* (2001, p. 68; italics added).

The identification of biology with Peircean semiosis was also accepted by Hoffmeyer, who expressed it with the idea that the basic unit of life is the sign, not the molecule. A similar concept was expressed by Kull in no uncertain terms*: "Sign science and life science are coextensive"*; *"semiotics is biology and biology is semiotics"* (Kull 2001, p. 3; italics added).

The Issue of Mechanism

In March 2001 I sent to Thomas Sebeok the first version of *The Organic Codes*, a manuscript in which I pointed out that there are many organic codes in nature, and that their appearance in the history of life was associated with the great events of macroevolution. I also argued that the existence of the organic codes requires that we introduce in biology not only the concept of *information*, but also the concept of *meaning*.

Sebeok kindly acknowledged the manuscript and a few weeks later invited me to review a special issue of *Semiotica* edited by Kull and entitled "Jakob von Uexküll: A Paradigm for Biology and Semiotics" (Kull 2001). I accepted with enthusiasm at first, but soon became aware of a sharp contrast between our positions. In my book I had stressed that organic meaning comes from coding, whereas all contributors to the special issue were endorsing the Peircean view that meaning is always produced by a process of interpretation. Such a contrast could hardly be ignored, and in my review I pointed out that the crucial point is the position that we take on the issue of *mechanism*.

The endorsement of a non-mechanistic approach to life was indeed a constant underlying theme of the special issue, and biosemiotics was portrayed as the crowning achievement of the idealistic tradition that goes back to Goethe, von Baer, Driesch, and Uexküll. I argued instead that the existence of organic codes and organic meaning in nature are scientific problems that can and should be investigated with the classical method of science, i.e., the mechanistic approach of model building.

In fact, "understanding" something very often means explaining it with a model that we are familiar with, and a machine gives us an immediate sense of familiarity. When we see it working before our eyes, we feel that we "know" it. Actually, we do not even need to build a machine to get this feeling. A description is enough, and so a machine is often a *model*, or even an *algorithm*. One of the most famous machines of all time was built by Turing with just pencil and paper. A model, furthermore, does not necessarily have a mathematical form. Natural selection, for example, is a mechanistic model that is entirely expressed in words.

Mechanism, in short, is the view that scientific knowledge is obtained by building machine-like models of what we observe in nature and has at least four important features: (1) Mechanism is not *reductionism*, because a machine is a machine not when it is reduced to pieces but when it is put together into a working whole. (2) Mechanism is not *determinism*, because it is more general than classical physics (quantum theory is mechanism, and so is relativity, non-equilibrium thermodynamics, and the like). (3) Mechanism is not *physicalism*, because it is not limited to physical quantities (natural selection, the Turing machine, and Gödel's theorem are mechanistic models that are not based on physical quantities). (4) Finally, and most importantly, mechanism is made of models, and models do not coincide with reality ("the map is not the territory"), which means that mechanism is intrinsically incomplete and continuously evolving.

Mechanism, in short, is virtually equivalent to the scientific method. The difference is that the *hypotheses* of the scientific method are replaced by *models*, i.e., by descriptions of fully functional working systems. Mechanism, in other words, is *scientific modeling*.

Ever since its first appearance at the beginning of the scientific revolution, mechanism has been highly effective in problem solving, and at the same time it has shown an extraordinary ability to change in the face of adversity. The first mechanistic model of the body was the clock-machine, then came the steam engine, and after that the computer—which amounts to saying that mechanism has introduced in biology first *mechanical energy*, then *chemical energy*, and finally *information*. Now we face a new challenge, and mechanism may well be able to change again and introduce in biology not only the concepts of energy and information, but also the last frontier, the concept of *meaning*.

I concluded my review by saying that

> the first two main points of this special issue—the making of biosemiotics and the recovery of Jakob von Uexküll from oblivion—come out with clarity and force, and are definitely a success. Unfortunately, however, there is also a third less happy theme that is

developed throughout the volume. The endorsement of non-mechanism, or qualitative organicism, is in my opinion the first serious mistake of the young field of biosemiotics. Indeed it is the one drawback that can prevent it from growing into a true science. I must conclude therefore that biosemiotics has not yet come of age, but I do hope that this criticism is taken for what it is: a diagnosis that is supposed to help, not to hurt. (Barbieri 2002, pp. 294–295)

A Pluralistic Enterprise

I sent my review to Thomas Sebeok in August 2001, saying that I had not been able to write an impartial report, and that therefore I would not be surprised if he turned it down. Surprisingly, however, Sebeok accepted it, and I received a copyright transfer form to fill in. That gave me the idea to test his determination, so I answered that I needed to keep the copyright to myself for a forthcoming book. Since he had been taken ill, it was his wife Jean who replied and wrote that "he has made some rare exceptions to the copyright rule when necessary, and he would be willing to do so in this case." That convinced me that Sebeok *wanted* to publish my review, and this meant that he was not *in principle* against a mechanistic approach to the problem of meaning.

Sebeok died a few months later, on December 21, 2001, and my review appeared in *Semiotica* the following year (Barbieri 2002). Personally, I took it as an invitation to join the biosemiotic community and to argue in favor of a mechanistic approach from within that community. I decided therefore to give it a try and asked to take part in the second Gathering in Biosemiotics in Tartu, Estonia, in June 2002. There I found a genuine attention to novel ideas and willingness to discuss them without the constraint of ideological principles. Gone were the triumphal tones and the neo-vitalistic declarations of the special issue, and I came away with the feeling that nothing had been settled yet, that everything was on the move. I had the same impression a year later, at the third Gathering in Copenhagen, and realized that a dialogue could start between us over the problem of meaning in nature. At the same time, I became aware that our discussions were not enough. We needed to reach out to a larger audience, and that is why, in March 2004, I proposed to create a new journal specifically dedicated to biosemiotics.

The agreement was reached in June 2004, at the fourth Gathering organized by Anton Markoš in Prague. Claus Emmeche, Hoffmeyer, Kull, Markoš, and I met in a pub and decided that what united us—the introduction of meaning in biology—was far more important than our divisions. Up until then, I had been referring to the study of biological meaning as *semantic biology*, whereas Markoš was calling it *biohermeneutics*, but we agreed to give up those favorite names of ours and to adopt the term *biosemiotics* that Sebeok had been campaigning for with so much passion and vigor. At the same time, I underlined that our differences did not have to be suppressed, and different schools of biosemiotics could, and should, coexist. The building of biosemiotics, in other words, had to be a pluralistic enterprise, and we all agreed on this point.

The practicalities of looking for a publisher, testing the market, and collecting a critical mass of papers took a few years, but eventually I signed a contract with Springer as editor-in-chief of *Biosemiotics*, and a second contract as co-editor, with Jesper Hoffmeyer, of a Springer Book Series in Biosemiotics. Journal and book series started publishing in 2008, and have appeared regularly ever since.

My editorial position, on the other hand, was not preventing me from developing the scientific approach to the problem of meaning, and in particular the idea that organic meaning is produced by coding, not interpretation. This is the key idea of an approach that started with the name of *Code Biosemiotics*, and later evolved into *Code Biology*, as I shall describe in the rest of this letter.

An Objective Criterion

The first problem that we need to solve in our investigation is the experimental reality of the organic codes, and to this purpose we need an objective criterion that allows us to make tests that prove whether or not organic codes do exist in Nature. The starting point is the idea that a code is always *a set of rules that establish a correspondence between two independent worlds* (Barbieri 2003). Morse code, for example, is a correspondence (or a *mapping*) between the letters of the alphabet and groups of dots and dashes; the highway code is a correspondence between street signals and driving behaviors, and so on.

What is essential in all codes is that *the coding rules are not dictated by the laws of physics and chemistry*. In this sense they are *arbitrary*, and the number of arbitrary relationships between two independent worlds is potentially unlimited. In Morse code, for example, any letter of the alphabet could be associated with countless combinations of dots and dashes, which means that a specific link between them can be realized only by selecting a small number of rules. And this is precisely what a code is*: a small set of arbitrary rules selected from a potentially unlimited number in order to ensure a specific correspondence between two independent worlds*.

In biology, organic codes are relationships between two worlds of organic molecules, and are necessarily implemented by other molecules, called *adaptors*, that build a bridge between them. The adaptors are required because there is no necessary link between the two worlds, and a fixed set of adaptors is required in order to guarantee the specificity of the correspondence (Barbieri 2003). The adaptors, in short, are essential in all organic codes. They are the molecular *fingerprints* of the codes, and their presence in a biological process is a sure sign that this process is based on a code.

This gives us an *objective* criterion for the discovery of organic codes, and their existence in Nature is no longer a matter of speculation. It is first and foremost an experimental problem. More precisely, we can prove that an organic code exists if we prove the existence of three entities: (1) two independent worlds of molecules; (2) a potentially unlimited number of arbitrary connections between them implemented by adaptors; and (3) a selection of adaptors (a set of coding rules) that ensures a specific correspondence.

Let us illustrate this criterion with two outstanding examples.

The Genetic Code

In protein synthesis, a sequence of nucleotides is translated into a sequence of amino acids, but it has been shown that there is no necessary link between nucleotides and amino acids. These molecules belong to two independent worlds, and a bridge between them is realized by a third type of molecules, called *transfer-RNAs*, which act as adaptors and perform two distinct operations: at one site they recognize groups of three nucleotides, called *codons*, and at another site they receive amino acids by enzymes called *amino-acyl-synthetases*. The key point is that a binding between synthetases and transfer-RNAs can be realized in countless different ways, and this means that in principle any amino acid can be associated with any codon. The number of connections, in other words, is potentially unlimited, and only the selection of a small fixed set of adaptors can ensure a specific mapping. This is *the genetic code*: a fixed set of rules of correspondence between codons and amino acids that are implemented by adaptors.

The Signal Transduction Codes

Signal transduction is the process by which cells transform the signals from the environment, called *first messengers*, into internal signals, called *second messengers*. The key point is that the molecules that perform the transduction are true adaptors. They consist of three subunits: a *receptor* for the first messengers, an *amplifier* for the second messengers, and a *mediator* in between (Berridge 1985). This allows the transduction complex to perform two independent recognition processes, one for the first messenger and the other for the second messenger. Laboratory experiments have proved that any first messenger can be associated with any second messenger, which means that there is a potentially unlimited number of arbitrary connections between them. In signal transduction, in short, we find all three essential components of a code: (1) two independent worlds of objects (first messengers and second messengers); (2) a potentially unlimited number of arbitrary connections produced by adaptors; and (3) a set of coding rules (a selection of the adaptors) that ensures the specificity of the correspondence (Barbieri 2003).

A World of Organic Codes

It is still a widely diffused opinion these days that the genetic code and the codes of culture make up the totality of the codes of Nature, but in reality many other organic codes (codes between organic molecules) have been discovered in the past few decades.

In 1975, the American biochemist Gordon Tomkins published a paper entitled “The Metabolic Code: Biological Symbolism and the Origin of Intercellular Communication.” That was the very first announcement of a new organic code after the discovery of the genetic code, but tragically Tomkins died that very year and his new world of organic symbolism remained unexplored. Some ten years later, Edward Trifonov started a lifelong campaign in favor of the idea that genomes carry several overlapping codes simultaneously (and not just the classic triplet code), and gave them the collective name of *sequence codes* (Trifonov 1987, 1989, 1999).

Finally, at the end of the 1990s and in the early 2000s, a whole new world of organic codes came to light. Among them: the *adhesive code* (Readies and Takeichi 1996; Shapiro and Colman 1999), the *splicing codes* (Barbieri 1998, 2003; Pertea et al. 2007; Barash et al. 2010; Dhir et al. 2010), the *signal transduction codes* (Barbieri 1998, 2003), the *sugar code* (Gabius 2000, 2009), the *histone code* (Strahl and Allis 2000; Turner 2000, 2002, 2007), the *cytoskeleton* and the *compartment codes* (Barbieri 2003), the *neural code* (Nicolelis and Ribeiro 2006; Osborne et al. 2008), the *tubulin code* (Verhey and Gertig 2007), the *nuclear signaling code* (Maraldi 2008), and the *ubiquitin code* (Komander and Rape 2012).

It must be pointed out that codes have been defined in different ways, a problem that is not uncommon in biology. But in our case a solution does exist because, as we have seen, there is an operational definition that can be applied to all organic codes.

What is particularly important is that the existence of many organic codes in Nature is not only a major experimental fact. It is one of those facts that have extraordinary theoretical implications. The first is that the great events of macroevolution were associated with the appearance of new organic codes, an idea that gives us a completely new understanding of the history of life.

Origin and Evolution of Cells

The data from molecular biology have revealed that all known cells belong to three distinct primary kingdoms, or domains, that Woese (1987, 2000) called *Archaea*, *Bacteria*, and *Eukarya*. The fact that virtually all cells have the same genetic code means that this code appeared in primitive systems that are collectively known as the *common ancestor*. But how did the common ancestor give origin to the cells of the three primary kingdoms? A good clue comes from the fact that all cells have a context-dependent behavior because they regulate protein synthesis according to the signals that come from the environment (Jacob and Monod 1961). This means that a signal transduction code was of paramount importance to the ancestral systems, which makes it very likely that they made various attempts to develop it.

It is an experimental fact, at any rate, that Archaea, Bacteria, and Eukarya have three different types of membranes, and three distinct signaling systems. This suggests that the three domains came into being by combining the universal genetic code with three distinct signal-transduction codes. This amounts to saying that the genetic code was instrumental to the origin of the common ancestor, and that the signal transduction codes were instrumental to the origin of the first cells.

In order to understand the evolution of the first cells we need to keep in mind that bacteria appeared very early on our planet, and some of them have remained substantially the same ever since. This is dramatically illustrated by the fact that modern stromatolites built by cyanobacteria are virtually identical to the 3.4 and to the 1.8 billion-year-old stromatolites that have been found in the fossil record (Schopf 1999; Knoll 2003). Primitive bacteria, in other words, already had the main characteristics of their modern descendants, and this tells us something important about the early history of life. It tells us that the descendants of the common ancestor had two evolutionary strategies in front of them, one based on increasing simplification, or *streamlining*, and one based on increasing complexity.

The cells that adopted a streamlining strategy got rid of all unnecessary components, lost the ability to evolve new organic codes, and have remained substantially the same ever since. Other cells conserved their primitive features, including the potential to evolve new organic codes, and have become increasingly complex. This tells us that codes lie at the very heart of the evolutionary mechanism. The cells that did not evolve new organic codes became *bacteria* and have never changed their fundamental structure. The cells that evolved new codes, such as splicing codes, cytoskeleton codes, compartment codes, histone code, and so on, became *eukarya* and have generated increasingly complex cellular organizations.

We realize in this way that there is a close association between the great events of macroevolution and the appearance of new organic codes, and we can also understand why. It is because a new code can bring into existence something that has never existed before, because the adaptors of an organic code create arbitrary associations. Any new organic code, in conclusion, produces a genuine increase in complexity, to the point that the best measure of the complexity of a living system is probably the number of its codes.

Organic Semiosis

Semiosis is *the production of signs*, and semiotics is usually referred to as *the study of signs* (from the Greek *semeion* = sign); but these definitions are too restrictive because signs are always associated with other entities. A sign, to start with, is always linked to a *meaning*. As living beings, we have a built-in drive to make sense of the world, to give meanings to things, and when we give a meaning to something, that something becomes a sign for us. Sign and meaning, in other words, cannot be taken apart because they are the two sides of the same coin. Semiotics, therefore, is not just the study of signs; it is the study of signs and meanings together. The result is that a system of signs, i.e., a *semiotic system*, is always made of at least two distinct worlds: a world of entities that we call *signs*, and a world of entities that represent their *meanings*.

A code, as we have seen, is a set of rules that establish a correspondence between the objects of two independent worlds. Let us observe now that establishing a correspondence between, say, object 1 and object 2, is equivalent to saying that object 2 is the meaning of object 1. In Morse code, for example, the rule that "dot-dash" corresponds to the letter "A" is equivalent to saying that the letter "A" is the meaning of "dot-dash." In English, the mental object of the sound "apple" is associated with the mental object of the fruit "apple," and this is equivalent to saying that this fruit is the meaning of that sound.

By the same token, the rule of the genetic code that a group of three nucleotides (a codon) corresponds to an amino acid is equivalent to saying that that amino acid is the *organic meaning* of that codon. Anywhere there is a code, be it in the mental or in the organic world, there is meaning (Barbieri 2003). All we need to keep in mind is that *meaning is a mental entity when the code is between mental objects, and an organic entity when the code is between organic molecules*.

This tells us that meaning is often produced by codes, but we know that in animals it is also produced by processes of interpretation, and this suggests that that there are at least two distinct types of semiosis in life, one based on coding and one based on interpretation. According to Peirce, however, interpretation is a defining feature of semiosis and is necessarily present in all its forms.

Sebeok extended semiosis from animals to all living creatures on the grounds that free-living single cells like bacteria and protozoa display *context-dependent* behavior, and apparently he was convinced that such behavior requires the ability to interpret the signals from the environment.

In reality, the context-dependent behavior of single cells is accounted for much more naturally by the combination of two or more organic codes. A context-dependent behavior means a context-dependent expression of genes, and this is obtained simply by linking gene expression to signal transduction, i.e., by coupling the genetic code with a signal transduction code. It takes only two context-free codes, in short, to produce a context-dependent behavior. Coding and decoding, on the other hand, are far simpler than interpretation, and there is no need to assume anything more complicated than that in free-living single cells, especially in those that appeared at the beginning of the history of life.

For all their outstanding abilities in coding and decoding, however, single cells do not build internal representations of the world and therefore cannot interpret them. They are sensitive to light, but do not "see"; they react to sounds but do not "hear"; they detect hormones but do not "smell" or "taste" them. It takes the cooperation of many cells that have undertaken specific processes of differentiation to allow a living system to see, hear, smell, and taste, so it is only multicellular creatures that have these experiences.

Free-living single cells are semiotic creatures because they make use of signs; but their semiosis is based exclusively on organic codes, and for this reason it has been referred to as *organic semiosis*. There simply is no evidence of interpretation at the molecular level. One of the best proofs of this comes from the fact that the genetic code has been highly conserved in all living organisms and in all environments ever since the origin of life, which clearly means that it does not depend on interpretation.

Animal Semiosis

The origin of animals is described as the origin of multicellular creatures that evolved a nervous system and acquired what we call feelings, sensations, perceptions, mental images, and so on. The transformation of the signals received by the sense organs into mental images, or high-level neural states, is based on sets of rules that are often referred to as *neural codes*, because neurobiology has made it abundantly clear that there are no necessary connections between sensory inputs and mental, or neural, images. This suggests that the appearance of different neural codes in the evolution of the brain is comparable to the appearance of different organic codes in the evolution of the cell, both starting from a virtually universal original code.

Such a scenario, however, turns out to be only partially true. The increase in the number of neural codes would explain the increase in complexity that took place in brain evolution, but would produce animals whose behavior is almost entirely pre-programmed, or *hardwired*, because codes are based on fixed rules. As a matter of fact, many animals (for example fishes) do have virtually hardwired reactions, and in those cases animal behavior is indeed largely accounted for by neural codes only. At the same time, however, it is a fact that some animals evolved the ability to *interpret* what goes on in the world around them, and this skill is a true evolutionary novelty, something that is not reducible to coding.

Interpretation is the ability to reach a conclusion from sensory inputs whose result can vary according to circumstances, memory, experience, and learning. In a way, it is the ability to "jump-to-conclusions," so to speak, from a limited number of data, with results that may not be perfect but are good enough for the purpose of survival. This "extrapolation from limited data" is not reducible to the classical Aristotelian categories of induction and deduction, and for this reason Peirce called it *abduction*. It is a new logical category, and the ability to interpret the world appears to be based precisely on that logic. Interpretation, in short, is a form of semiosis because it involves signs and meanings, but it is different from organic semiosis because it is not based on coding but on abduction.

Interpretation, furthermore, is a faculty that did not appear full-blown in animals, but evolved in stages, and we can still see intermediate forms of its historical evolution. Some animals (like snakes), for example, stop chasing a prey when it disappears from sight, whereas others (like mammals) deduce that the prey has temporarily been hidden by an obstacle and continue chasing it. Some can even learn to follow the footsteps of a prey, which reveals a still higher degree of abstraction (Barbieri 2011).

What animals interpret, furthermore, is not the world but *representations* of the world, and neural representations are formed by neural networks made of many different types of cells, which means that interpretation can exist only in multicellular systems.

The evolution from single cells to animals, in conclusion, was far more than an increase in growth and complexity. It was a true macroevolution that gave origin to absolute novelties, to entities that did not exist before, such as perceptions, feelings, and the ability to interpret what goes on in the surrounding world. This is what divided animals from single cells, and this is why there are at least two distinct types of semiosis in living systems: one based on coding and decoding (*organic semiosis*) and one based on interpretation (*animal semiosis*).

Two Types of Biosemiotics

The *manifesto* written by Sebeok and colleagues (1984) declared that the semiotics of Peirce is a "paradigm for biology," a theoretical framework that illuminates the life sciences because it provides them with entirely new concepts. Hence followed the project of introducing Peircean concepts in biology, a project that a few years later Sebeok referred to as *biosemiotics*, the synthesis of biology and semiotics (Sebeok and Umiker-Sebeok 1992).

Ever since 2001, when Sebeok asked me to review a special issue of *Semiotica* dedicated to Uexküll, I have voiced a specific criticism to that project. I repeatedly argued that a synthesis of biology and semiotics can and should be a *scientific* research project, aimed at *discovering* which semiotic processes actually take place in living systems. On this point, furthermore, I underlined that the existing data allow us to reach three major conclusions.

Standard scientific tests prove that organic codes exist in single cells. This amounts to saying that there is in Nature a form of semiosis that is based exclusively on coding and decoding (*organic semiosis*).

There is good evidence that some ancestral animals started evolving the ability to interpret what goes on in the world around them, and this makes us realize that there is in Nature a second form of semiosis that is based on coding and interpretation (*animal semiosis*).

Finally, impressive data show that a third type of semiosis evolved in our species, a semiosis that is based on coding, interpretation, and language (*human semiosis*).

The journal *Biosemiotics* started publishing in 2008, and since then I made annual surveys of the opinions expressed by the authors of papers, by the members of the editorial board, and by the participants in the Gatherings in Biosemiotics. The results turned out to be a complete surprise to me. Most biosemioticians acknowledged that what we find in single cells is only coding and decoding, but maintained that cells are nevertheless capable of interpretation *because we can define decoding as a form of interpretation*. There are countless examples of this trick in the literature, and the following are just two of them.

In the paper "What Does It Take to Produce Interpretation?" Brier and Joslyn (2012, p. 154) proposed solving the problem in this way:

> we can identify *interpretation* in general as any process which encounters a sign and takes it for its meaning in virtue of some code. … Thus *a ribosome is an interpreter*. And the right amino acid is its interpretation of some codon.

And in the paper "Anticipatory Functions, Digital-Analog Forms and Biosemiotics," Arnellos et al. (2012, p. 353) offered a Peircean description of signal transduction and wrote that "*receptors act as interpreting systems* by coupling to transducers catalytic molecules that trigger the production of another sign inside the cell in response to the extracellular sign."

Here we are then. One can say that all cells are interpretive systems simply by adopting an ad hoc definition of interpretation. Words, after all, are tools that we employ for our own purposes, and we are used to giving them multiple meanings, so where is the problem?

The problem is not the use of words, which are indeed tools, but the result that we obtain with them, and in our case, the result is two very different types of biosemiotics:

(1) Peircean biosemiotics is essentially a reformulation of known biological processes in Peircean terms. It describes living systems with new words but does not discover anything new about them.
(2) Only a scientific approach to biosemiotics can lead to genuine discoveries, but requires that we learn from experiments, not from ad hoc definitions, what the semiotic properties of Nature are.

The surveys made regular assessments of these two positions for four years, and in the end it turned out that roughly 90 % of the biosemioticians were supporting the Peircean approach. In principle, one could still argue that there are two types of biosemiotics, but in practice it was obvious that this was no longer the case.

Facing Reality

Thomas Kuhn argued that "a paradigm corresponds not to a subject matter but rather to a group of *practitioners*," (Kuhn 1962, pp. 179–180). A similar thesis was later expressed by Mihaly Csikszentmihalyi (1996, p. 28), who stressed that a research field "includes all the individuals who act as *gatekeepers* to the domain. It is their job to decide whether a new idea or product should be included in the domain."

According to these views, a discipline is what its gatekeepers say it is, and in this sense the identification of biosemiotics with *Peircean biosemiotics* was a perfectly legitimate operation because the board of the International Society for Biosemiotic Studies (ISBS) consisted almost exclusively of Peirce followers.

There was also another reason for that conclusion. Semiotics has become today a highly influential discipline, and the "Peirce industry" has grown into an impressive enterprise that, like the "Darwin industry" in biology, is producing a steady flow of books, journals, congresses, grants, and university positions. Like many other disciplines, on the other hand, semiotics is subdivided into "niches," one of which is precisely its applications in biology. In Academia, as in Nature, all niches tend to be occupied, and this is why the relationship between semiosis and biology has become an increasingly active area in recent years. More than that: many semioticians openly underlined "how exciting" for them was the thought of "contributing to the study of life," of "building a new paradigm for biology," and this goes a long way to explaining why virtually all semioticians were endorsing the Peircean approach in biosemiotics.

The surveys also brought to light another explanation. The scientists who were supporting the Peircean approach were often using the arguments employed by the supporters of *intelligent design*. In retrospect this is hardly surprising, because "interpretation" is indeed a form of "intelligence," and Peirce himself promoted the idea that there is an "extended mind" in the universe. The difference between the two cases is that in intelligent design the "interpreting agency" is outside Nature, whereas in Peircean biosemiotics it is inside it. The common factor is that in both cases all facts of science are reinterpreted in a "postmodern" framework simply by changing the meaning of a few key words.

By 2012, the surveys made it abundantly clear that most scholars and researchers identify biosemiotics with Peircean biosemiotics, a paradigm that is extending a cultural model of semiosis to the whole of Nature rather than discovering from Nature what biological semiosis actually is. It also became painfully clear that a scientific approach to the semiosis of Nature could not prosper within that framework, and that its future was seriously at risk.

This is why, at the end of 2012, I resigned as editor-in-chief of *Biosemiotics*, and together with eleven colleagues (Jan-Hendrik Hofmeyr, Peter Wills, Almo Farina, Stefan Artmann, Joachim De Beule, Peter Dittrich, Dennis Görlich, Stefan Kühn, Chris Ottolenghi, Liz Swan, and Morten Tønnessen) founded the International Society of Code Biology (ISCB). We also decided to leave no doubt about the scientific nature of our project, and to this end we explicitly wrote in the constitution of the new society that Code Biology is "the study of all codes of life *with the standard methods of science.*"

Code Biology

The genetic code appeared on Earth at the origin of life, and the codes of culture arrived almost four billion years later, at the end of life's history. It is still widely believed today that these are the only codes that exist in Nature, and if this were true we would have to conclude that codes are *extraordinary exceptions* because they appeared only at the beginning and at the end of evolution. In reality, various other organic codes have been discovered in the recent past, and it is likely that many more will be discovered in the future. This is the vast new research field of Code Biology: the study of all codes of life, and in particular of the codes that appeared *after* the genetic code and *before* the codes of culture.

It is important to underline that the existence of many organic codes in Nature has direct implications not only for the history of life, but also for our understanding of the *logic* of life (Barbieri 2013). Molecular biology has shown that the *copying* of genes and the *coding* of proteins are the two fundamental mechanisms of life, and now the discovery of many other organic codes makes us realize that coding is the key mechanism that brought into being not only proteins but many other biological novelties as well.

In modern biology the cell is described as an *autopoietic* system, a "system that fabricates itself," and autopoiesis, the ability of the cells to produce their own components, and eventually to produce copies of themselves, is regarded as the key process of life. At a closer look, however, this is not always what happens. In embryonic development, for example, the cells produce cells that are normally *different* from their progenitors. Most importantly, specific proteins did not exist before the origin of the genetic code, and the ancestral systems were producing descendants that were inevitably *different* from themselves. Autopoiesis, in other words, was not present before the first cells, so it was not the mechanism that gave origin to them.

Before the genetic code, the ancestral ribonucleoprotein system of the common ancestor was engaged in the process of evolving coding rules, and was therefore a *code-generating system*. After the genetic code, however, the situation changed dramatically. No other modification in coding rules was accepted, and the system in question became a *code conservation system*. Another part of the system, however, maintained the potential to evolve other coding rules, and behaved as a new *code generating,* or *code exploring, system*.

In early Eukarya, for example, the cells had *a code conservation part* for the genetic code, but also a *code-exploring part* for the splicing code. The origin of the first cells, in short, was based on the ability of the ancestral systems to *generate* the rules of the genetic code, and the subsequent evolution of the cells was based on two complementary processes: the *generation* of new organic codes and the *conservation* of the existing ones. Taken together, these two processes are the two complementary sides of a biological phenomenon that has been referred to as "codepoiesis" (Barbieri 2012).

In conclusion, the ancestral systems that gave origin to the first cells were not autopoietic systems but had to be codepoietic systems. And all the cells that came after them were not always engaged in autopoiesis, but were inevitably engaged in codepoiesis. What is always and necessarily present in all living systems, in other words, is codepoiesis, and this gives us a new model of the cell that can be expressed in this way: *the cell is a codepoietic system, i.e., a system that is capable of creating and conserving its own codes*.

Codepoiesis accounts for the two most important events that took place in evolution. The ability to create coding rules accounts for the origin of the genetic code and of all the other codes that followed. The ability of the cell to conserve its own codes accounts for the fact that the organic codes are *the great invariants of life*, the sole entities that have been conserved in evolution while everything else has changed.

This makes us realize that Code Biology, the study of all codes of life, is also the study of the *deep logic* of life, the exploration of a still largely unknown dimension of life, the real new frontier of biology.

References

Anderson M, Deely J, Krampen M, Ransdell J, Sebeok TA, von Uexküll T (1984) A semiotic perspective on the sciences: steps toward a new paradigm. Semiotica 52:7–47

Arnellos A, Bruni LE, El-Hani CN, Collier J (2012) Anticipatory functions, digital-analog forms and biosemiotics. Biosemiotics 5:331–367

Barash Y, Calarco JA, Gao W, Pan Q, Wang X, Shai O, Blencow BJ, Frey BJ (2010) Deciphering the splicing code. Nature 465:53–59

Barbieri M (1998) The organic codes: the basic mechanism of macroevolution. Riv Biol Biol Forum 91:481–514

Barbieri M (2002) Has biosemiotics come of age? Semiotica 139:283–295

Barbieri M (2003) The organic codes: an introduction to semantic biology. Cambridge University Press, Cambridge

Barbieri M (2011) Origin and evolution of the brain. Biosemiotics 4:369–399

Barbieri M (2012) Codepoiesis: the deep logic of life. Biosemiotics 5:297–299

Barbieri M (2013) The paradigms of biology. Biosemiotics 6:33–59

Berridge M (1985) The molecular basis of communication within the cell. Sci Am 253(4):142–152

Brier S, Joslyn C (2012) What does it take to produce interpretation? Biosemiotics 6:143–159

Csikszentmihalyi M (1996) Creativity: flow and the psychology of discovery and innovation. Harper Collins, New York

de Saussure F (1916) Cours de linguistique générale. Payot, Paris

Dhir A, Buratti E, van Santen MA, Lührmann R, Baralle FE (2010) The intronic splicing code: multiple factors involved in ATM pseudoexon definition. EMBO J 29:749–760

Favareau D (2007) The evolutionary history of biosemiotics. In: Barbieri M (ed) Introduction to biosemiotics. Springer, Dordrecht, pp 1–67

Florkin M (1974) Concepts of molecular biosemiotics and molecular evolution. In: Florkin F, Stotz EH (eds) Comprehensive biochemistry, vol 29A. Elsevier, Amsterdam, pp 1–124

Gabius H-J (2000) Biological information transfer beyond the genetic code: the sugar code. Naturwissenschaften 87:108–121

Gabius H-J (2009) The sugar code. Fundamentals of glycosciences. Wiley-Blackwell, Weinheim

Jacob F, Monod J (1961) Genetic regulatory mechanisms in the synthesis of proteins. J Mol Biol 3:318–356

Knoll AH (2003) Life on a young planet: the first three billion years of evolution on Earth. Princeton University Press, Princeton

Komander D, Rape M (2012) The ubiquitin code. Annu Rev Biochem 81:203–229

Krampen M (1981) Phytosemiotics. Semiotica 36:187–209

Kuhn TS (1962) The structure of scientific revolutions. Chicago University Press, Chicago

Kull K (ed) (2001) Jakob von Uexküll: a paradigm for biology and semiotics. Semiotica vol 134(1/4). Mouton de Gruyter, Berlin

Maraldi NM (2008) A lipid-based code in nuclear signalling. In: Barbieri M (ed) The codes of life: the rules of macroevolution. Springer, Dordrecht, pp 207–221

Nicolelis M, Ribeiro S (2006) Seeking the neural code. Sci Am 295(6):70–77

Osborne LC, Palmer SE, Lisberger SG, Bialek W (2008) The neural basis for combinatorial coding in a cortical population response. J Neurosci 28:13522–13531

Peirce CS (1906) The basis of pragmaticism. In: Hartshorne C, Weiss P (eds) The collected papers of Charles Sanders Peirce, vol I. Harvard University Press, Cambridge, pp 1931–1935

Pertea M, Mount SM, Salzberg SL (2007) A computational survey of candidate exonic splicing enhancer motifs in the model plant *Arabidopsis thaliana*. BMC Bioinform 8:159

Posner R, Robering K, Sebeok TA (1997) Semiotik/Semiotics: a handbook on the sign-theoretical foundations of nature and culture, vol 1. Walter de Gruyter, Berlin

Readies C, Takeichi M (1996) Cadherine in the developing central nervous system: an adhesive code for segmental and functional subdivisions. Dev Biol 180:413–423

Schopf JW (1999) Cradle of life: the discovery of Earth's earliest fossils. Princeton University Press, Princeton

Sebeok TA (1963) Communication among social bees; porpoises and sonar; man and dolphin. Language 39:448–466

Sebeok TA (1972) Perspectives in zoosemiotics. Mouton, The Hague

Sebeok TA (2001) Biosemiotics: its roots, proliferation, and prospects. In: Kull K (ed) Jakob von Uexküll: A paradigm for biology and semiotics. Semiotica vol 134. Mouton de Gruyter, Berlin, pp 61–78

Sebeok TA, Umiker-Sebeok J (1992) Biosemiotics: the semiotic web. Mouton de Gruyter, Berlin

Shapiro L, Colman DR (1999) The diversity of cadherins and implications for a synaptic adhesive code in the CNS. Neuron 23:427–430

Strahl BD, Allis D (2000) The language of covalent histone modifications. Nature 403:41–45

Tomkins MG (1975) The metabolic code. Science 189:760–763

Trifonov EN (1987) Translation framing code and frame-monitoring mechanism as suggested by the analysis of mRNA and 16s rRNA nucleotide sequence. J Mol Biol 194:643–652

Trifonov EN (1989) The multiple codes of nucleotide sequences. Bull Math Biol 51:417–432

Trifonov EN (1999) Elucidating sequence codes: three codes for evolution. Ann NY Acad Sci 870:330–338
Turner BM (2000) Histone acetylation and an epigenetic code. BioEssays 22:836–845
Turner BM (2002) Cellular memory and the histone code. Cell 111:285–291
Turner BM (2007) Defining an epigenetic code. Nat Cell Biol 9:2–6
Verhey KJ, Gaertig J (2007) The tubulin code. Cell Cycle 6:2152–2160
von Uexküll J (1928) Theoretische biologie. Zweite Auflage. Julius Springer, Berlin
Woese CR (1987) Bacterial evolution. Microbiol Rev 51:221–271
Woese CR (2000) Interpreting the universal phylogenetic tree. Proc Natl Acad Sci USA 97:8392–8396