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REVIEW

Biosemiotics: a new understanding of life

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Abstract Biosemiotics is the idea that life is based on semiosis, i.e., on signs and codes. This idea has been strongly suggested by the discovery of the genetic code, but so far it has made little impact in the scientific world and is largely regarded as a philosophy rather than a science. The main reason for this is that modern biology assumes that signs and meanings do not exist at the molecular level, and that the genetic code was not followed by any other organic code for almost four billion years, which implies that it was an utterly isolated exception in the history of life. These ideas have effectively ruled out the existence of semiosis in the organic world, and yet there are experimental facts against all of them. If we look at the evidence of life without the preconditions of the present paradigm, we discover that semiosis is there, in every single cell, and that it has been there since the very beginning. This is what biosemiotics is really about. It is not a philosophy. It is a new scientific paradigm that is rigorously based on experimental facts. Biosemiotics claims that the genetic code (1) is a real code and (2) has been the first of a long series of organic codes that have shaped the history of life on our planet. The reality of the genetic code and the existence of other organic codes imply that life is based on two fundamental processes—copying and coding—and this in turn implies that evolution took place by two distinct mechanisms, i.e., by natural selection (based on copying) and by natural conventions (based on coding). It also implies that the copying of genes works on individual molecules, whereas the coding of proteins operates on collections of molecules, which means that different mechanisms of evolution exist at different levels of organization. This review intends to underline the scientific nature of biosemiotics, and to this purpose, it aims to prove (1) that the cell is a real semiotic system, (2) that the genetic code is a real code, (3) that evolution took place by natural selection and by natural conventions, and (4) that it was natural conventions, i.e., organic codes, that gave origin to the great novelties of macroevolution. Biological semiosis, in other words, is a scientific reality because the codes of life are experimental realities. The time has come, therefore, to acknowledge this fact of life, even if that means abandoning the present theoretical framework in favor of a more general one where biology and semiotics finally come together and become *biosemiotics*.

Keywords Biosemiotics · Evolution · Information · Codes · Meaning

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Introduction

Semiotics is the study of signs, and biosemiotics can be defined, therefore, as the study of signs in living systems. This is the 'literal' definition of the discipline, a version that can be referred to as *sign-based biosemiotics* because it is explicitly based on the concept of sign. Biosemiotics, however, can also be defined as the study of codes in living systems, a version that is referred to as *code-based biosemiotics.* There have been historical disputes between the two versions but, as we will see, they are not incompatible, and both share the idea that every living creature is a semiotic system, i.e., that semiosis (the production of signs) is fundamental to life. The evidence for this conclusion comes primarily from the genetic code,

but modern biology has never accepted it. The discovery of the genetic code has been universally recognized as one of the greatest scientific breakthroughs of all times but not as proof that semiosis exists at the molecular level. Modern biology has not accepted—let us repeat this—that the existence of the genetic code implies that every cell is a semiotic system. And this is no accident. The rejection of the semiotic nature of life has been, and continues to be, extremely widespread because it is the logical consequence of at least three concepts that lie at the very heart of modern biology.

1. The first is the model that describes the cell as a duality of genotype and phenotype, i.e., as a biological computer where genes provide the software and proteins the hardware. The crucial point is that a computer has codes but is *not* a semiotic system because its codes come from a 'codemaker', which is outside it. This makes it legitimate to say that cells too can have a code without being semiotic systems. All we need, for that conclusion, is the idea that the genetic code was assembled by natural selection, i.e., by a codemaker that is outside the cell just as the human mind is outside the computer.
2. The second basic concept is *physicalism*, the doctrine that everything in life, including signs and codes, is ultimately reducible to physical quantities. This implies that the genetic code is not a 'real' code but a linguistic expression that biologists have adopted simply because it was intuitively appealing. Deep down, according to this view, the genetic code is but a metaphor because all its features must be completely accounted for by physical quantities.
3. The third basic concept of modern biology is the belief that every biological novelty has been brought into existence by natural selection. The codes, be they organic or mental, are outstanding phenomena, but as long as they are not a mechanism of evolution, they do not account for anything fundamentally new. This conclusion is reinforced by the fact that the genetic code appeared at the origin of life, whereas the codes of culture arrived almost four billion years later. They came into being respectively at the beginning and at the end of life's history and are considered, therefore, as utterly exceptional phenomena, not as ordinary biological processes.

The genotype–phenotype model, physicalism, and natural selection are the three pillars of modern biology, and they are totally alien to the idea that semiosis is fundamental to life. This idea, therefore, can become part of biology only if we prove that all the above concepts can be replaced by more general ones. That is what biosemiotics is really about. It is about a new biological paradigm that gives us (1) a new model of the cell, (2) a real alternative to physicalism, and (3) a new mechanism of evolution. These are the great novelties of biosemiotics, and this review is dedicated almost exclusively to illustrating them. More precisely, Part 1 is dedicated to the semiotic structure of the cell, Part 2 to the nature of information and meaning, Part 3 to the organic codes, and Part 4 to the mechanisms of evolution, whereas Part 5 will give a brief overview of the present state of biosemiotics.

Part 1: the semiotic structure of the cell

The code model of semiosis

Semiotics is usually referred to as the study of signs (from the Greek *semeion* = sign), but this definition is 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*.

The link between sign and meaning, in turn, calls attention to a third entity, i.e., to their *relationship*. A sign is a sign only when it stands for something that is other than itself, and this *otherness* implies at least some degree of independence. It means that there is no deterministic relationship between sign and meaning. Different languages, for example, give different names to the same object precisely because there is no necessary connection between names and objects. A semiotic system, therefore, is not any combination of two distinct worlds. It is a combination of two worlds between which there is no necessary link, and this has an extraordinary consequence. It implies that a bridge between the two worlds can be established only by conventional rules, i.e., by the rules of a code. This is what qualifies the semiotic systems, what makes them different from everything else: *a semiotic system is a system made of two independent worlds that are connected by the conventional rules of a code*. A semiotic system, in conclusion, is necessarily made of at least three distinct entities: signs, meanings, and code.

Here, at last, we have a definition where it is stated explicitly that a code is an essential component of a semiotic system. It is the rules of a code that create a correspondence between signs and meanings, and we can

say, therefore, that an act of semiosis is always an act of coding, i.e., it is always a convention. More precisely, we can say that an elementary act of semiosis is a triad of 'sign, meaning, and convention', whereas a semiotic system is a whole set of signs and meanings that are linked together by all the various conventions that make up a code.

Signs, meanings, and conventions, however, do not come into existence of their own. There is always an 'agent' that produces them, and that agent can be referred to as a *codemaker* because it is always an act of coding that gives origin to semiosis. In the case of culture, for example, the codemaker is the human mind since it is the mind that produces the mental objects that we call signs and meanings and the conventions that link them together. We come in this way to a general conclusion that can be referred to as 'the code model of semiosis': *a semiotic system is a triad of signs, meanings and code that are all produced by the same agent, i.e., by the same codemaker.*

This conclusion is highly relevant to biology because it tells us precisely what we need to prove in order to show that the cell is a semiotic system. We need to prove that in every living cell there are four distinct entities: signs, meanings, code and codemaker.

The molecules of life

Modern biology is based on three extraordinary experimental facts: (1) the discovery that most biological structures and functions are ultimately due to *proteins*, (2) the discovery that the hereditary instructions for making proteins are carried by strings of nucleotides called *genes*, and (3) the discovery that genes are translated into proteins by a universal set of rules, which has become known as *the genetic code*.

These discoveries have confirmed that genes and proteins are the key molecules of life but have also revealed something totally unexpected about them. They have shown that genes and proteins differ from all other molecules not only because of their size, shape, or chemical composition but primarily because they are produced in a totally different way. In the inorganic world, the structure of molecules is determined by the bonds that exist between their atoms, i.e., by internal factors. In living systems, instead, genes are built by molecular machines which physically stick their nucleotides together following the order of a template which is external to the growing molecule. In a similar way, proteins are made by molecular machines which bind amino acids in the order prescribed by an external template of nucleotides.

Genes and proteins, in short, are assembled by molecular robots on the basis of outside instructions. They are *manufactured* molecules, as different from ordinary molecules as *artificial* objects are from natural ones. Indeed, if we accept the commonsense view that molecules are natural when their structure is determined *from within* and artificial when it is determined *from without*, then genes and proteins can truly be referred to as artificial molecules, as *artifacts made by molecular machines*. This in turn implies that all biological objects are artifacts, and we arrive at the general conclusion that *life is artifact-making*.

The discovery that genes and proteins are manufactured molecules has direct implications for the origin of life because it tells us that primitive molecular machines came into existence long before the origin of the first cells. The simplest molecular machines we can think of are molecules that could join other molecules together by chemical bonds, and for this reason we may call them *bondmakers*. Some could form bonds between amino acids, some between nucleotides, others between sugars, and so on. It has been shown, for example, that short pieces of ribosomal RNA have the ability to form peptide bonds, so it is possible that the first bondmakers were RNA molecules of small or medium-size molecular weights. Among the various types of bondmakers, furthermore, some developed the ability to join nucleotides together in the order provided by a template. Those bondmakers started making copies of nucleic acids, so we can call them *copymakers*.

In the history of life, molecular copying came into being when the first copymakers appeared on the primitive Earth and started copying nucleic acids. This implies that natural nucleic acids had already been formed by spontaneous reactions on our planet, but that was no guarantee of evolution. Only the copying of genes could ensure their survival and have long-term effects, so it was really the arrival of copymaking that set in motion the extraordinary chain of processes that we call evolution. The first Major Transition of the history of life (Maynard Smith and Szathmáry 1995) is generally described as the origin of genes, but it seems more accurate to say that it was the origin of molecular *copying*, or the origin of *copymakers*, the first molecular machines that started multiplying nucleic acids by making copies of them.

The genetic code

Proteins are the key building blocks of all living structures, as well as the engines of countless reactions that go on within those structures. For all their extraordinary versatility, however, there is one thing they cannot do. Unlike genes, they cannot be their own templates. It is simply not possible to make proteins by copying other proteins. The transition from natural to manufactured molecules, therefore, was relatively simple for genes but much more complex for proteins. Manufactured genes could be made simply by copying natural genes, and all that was required to that purpose were molecules which had a polymerase-like

activity. Manufactured proteins, instead, could not be made by copying, and yet the information to make them had to come from molecules that can be copied because only those molecules can be inherited. The information for manufacturing proteins, therefore, had to come from genes, so it was necessary to bring together a carrier of genetic information (a messenger RNA), a peptide-bondmaker (a piece of ribosomal RNA), and molecules that could carry both nucleotides and amino acids (the transfer RNAs). The first protein-makers, in short, had to bring together three different types of molecules (messenger, ribosomal, and transfer RNAs), and were, therefore, much more complex than copymakers.

The outstanding feature of the protein-makers, however, was not the number of components. It was the ability to ensure a specific correspondence between genes and proteins, because without it there would be no biological specificity, and without specificity there would be no heredity and no reproduction. Life, as we know it, simply would not exist without a specific correspondence between genes and proteins.

Such a correspondence would be automatically ensured if the bridge between genes and proteins could have been determined by stereochemistry, as one of the earliest models suggested, but that is not what happens in Nature. The bridge is always provided by molecules of transfer RNA, first called *adaptors*, that have two recognition sites: one for a group of three nucleotides (a *codon*) and another for an amino acid. In this case, a specific correspondence could still be guaranteed automatically if one recognition site could determine the other, but again that is not what happens. The two recognition sites of the adaptors are physically separated in space and are chemically independent. There simply is no necessary link between codons and amino acids, and a specific correspondence between them can only be the result of conventional rules. Only a real code, in short, could guarantee biological specificity, and this means that in no way the genetic code can be dismissed as a linguistic metaphor.

Protein synthesis arose, therefore, from the parallel evolutions of the translation apparatus and of the genetic code, and the final machine was a *code-and-template-dependent-protein-maker* or, more simply, a *codemaker*. The second Major Transition of the history of life is generally described as the origin of proteins, but it would be more accurate to say that it was the origin of codemaking, or the origin of codemakers, the first molecular machines that discovered molecular coding and started populating the Earth with codified proteins.

The cell as a trinity

The idea that life is based on genes and proteins is often expressed by saying that every living system is a duality of genotype and phenotype. This model was proposed by Wilhelm Johannsen in 1909, but was accepted only in the 1940s and 1950s when molecular biology discovered that genes are chemically different from proteins and, above all, when it became clear that genes carry linear information, whereas proteins function by their three-dimensional structures. The genotype–phenotype duality is, therefore, a dichotomy that divides not only two different biological functions (heredity and metabolism) but also two different natural entities (information and energy). It is the simplest and most general way of defining a living system and has become the foundational paradigm of modern biology, the scheme that transformed the *energy-based* biology of the 19th century into the *information-based* biology of the 20th.

In the 1950s and 1960s, however, the study of protein synthesis revealed that genes and proteins are not formed spontaneously in the cell but are manufactured by a system of molecular machines based on RNAs. In 1981, the components of this manufacturing system were called *ribosoids*, and the system itself was given the collective name of *ribotype* (Barbieri 1981, 1985). The cell was described in this way as a structure made of genes, proteins, and ribosoids, i.e., as a trinity of genotype, phenotype, and ribotype.

This model is based on the conclusion that the ribotype had a historical priority over genotype and phenotype. Spontaneous genes and spontaneous proteins did appear on the primitive Earth but could not give origin to cells because they did not have biological specificity. They gave origin to copymakers and codemakers, and it was these molecular machines made of ribosoids that evolved into the first cells.

The RNAs and the proteins that appeared spontaneously on the primitive Earth produced a wide variety of ribosoids, some of which were synthetizing ribosoids, whereas others were ribogenes, and others were riboproteins (or ribozymes). The systems produced by the combination of all these molecules, therefore, had a ribotype, a ribogenotype, and a ribophenotype. Eventually, evolution replaced the ribogenes with genes and the riboproteins with proteins, but the synthetizing ribosoids of the ribotype have never been replaced. This shows not only that the ribotype is a distinct category of the cell but also that it is a category without which the cell simply cannot exist.

The ribosoids of the ribotype are the oldest phylogenetic molecules that exist on Earth (Woese 2000), and they firmly remain at the heart of every living cell. Genes, proteins, and ribosoids are all manufactured molecules, but only ribosoids can be also makers of those molecules. This concept can perhaps be illustrated by comparing the cell to a city where proteins are the objects, genes are the instructions, and ribosoids are the ‘makers’ of both objects and instructions, i.e., the inhabitants of the city.

It is an experimental fact, at any rate, that every cell contains a system of RNAs and ribonucleoproteins that makes proteins according to the rules of a code, and that system can be described, therefore, as a 'code-and-template-dependent-protein-maker' or more simply as a codemaker. That is the third party that makes of every living cell a trinity of genotype, phenotype, and ribotype. The genotype is the seat of heredity, the phenotype is the seat of metabolism, and the ribotype is the codemaker of the cell, the seat of the genetic code.

The defining feature of signs and meanings

A semiotic system is made of signs, meanings, code, and codemaker, and we know that there is a genetic code in protein synthesis. We also know that proteins are made by a system of ribonucleoproteins that is the physical seat of the genetic code and functions, therefore, as the codemaker of the cell. This tells us that every living cell does have a genetic code and a codemaker. But what about the other two entities? Can we say that there are also signs and meanings at the molecular level? Can these entities exist in the cell? In order to answer this question, let us examine first the traditional signs and meanings of culture and see if they have a qualifying feature that can be extended to the molecular level.

The signs and meanings that we are familiar with are often the mental representations of objects or events of the physical world. A sign, for example, can be a spoken word, and its meaning can be a mental image. The mental image of an object is normally evoked by different words in different languages, and this clearly shows that mental sounds and mental images are separable. When they are separated, however, they no longer function as signs and meanings. To a non-English speaker, for example, a word like 'twitch' may have no linguistic meaning, and in this case, it would be just a sound not a sign. There is no contradiction, therefore, in saying that signs and meaning are distinct mental objects, and that they cannot be taken apart because when they are taken apart, they simply stop functioning as signs and meanings.

This makes us understand an extremely important feature of semiosis. It tells us that a mental sign, or a mental meaning, is never an intrinsic property of a mental object. It is something that the mind can give to a mental object and that the mind can take away from it.

To this conclusion, one could object that terms like mental signs and mental objects are a clear case of *mentalism*, and that this is no longer the received view, today. The important point, however, is that the conclusion remains valid even if we accept that the sounds and images of our perceptions are just the results of neuron firings, and that the mind is but a product of the brain. Even in this case, the link between the neuron firings that produce the signs and the meanings of any language is based on the rules of a code and are totally dependent upon the agent of that code, i.e., upon the codemaker of the system.

Signs and meanings simply do not exist without a codemaker and outside a codemaking process. The codemaker is the agent of semiosis, whereas signs and meanings are its instruments. We conclude, therefore, that signs and meanings are totally dependent on codemaking, i.e., they are *codemaker-dependent entities*. This is the qualifying feature that we were looking for because it is completely general and can be applied to all systems. We can say, therefore, that signs and meanings exist at the molecular level, and in particular, in protein synthesis, only if we prove that in protein synthesis there are codemaker-dependent entities.

The sequences of genes and proteins

All biochemistry textbooks tell us that there is a genetic code in protein synthesis, but none of them mentions the existence of signs and meanings. At first sight, in fact, these entities do not seem to exist at the molecular level. The translation apparatus can be regarded as a codemaker because it is the seat of the code that creates a correspondence between genes and proteins, but these molecules appear to have only 'objective' chemical properties, not the 'codemaker-dependent' properties that *define* signs and meanings. A messenger RNA, for example, appears to be a unique and objective sequence of molecules, but let us take a closer look.

A messenger RNA is certainly a unique and objective chain of nucleotides, but in no way is it a unique sequence of codons because different codemakers could scan it in different ways. If the nucleotides were scanned two-by-two, for example, the sequence of codons would be totally different. The same chain of nucleotides, in other words, can give origin to many sequences of codons, and it is always the codemaker that determines the sequence because it is the codemaker that *defines* the codons. A linear sequence of codons, in short, does not exist without a codemaker and outside a codemaking process. It is totally dependent on codemaking and is, therefore, a codemaker-dependent entity, which is precisely what a sign is.

In the same way, the linear sequence of amino acids that is produced by the translation apparatus is also a codemaker-dependent entity because only a codemaker can produce it. Any spontaneous assembly of amino acids would *not* make linear chains, and above all, it would not arrange the amino acids in a specific order. Specific linear sequences of amino acids can be produced only by codemakers, but different codemakers would arrange the amino acids in different ways, which shows that the

sequence of a protein is only one of the many possible 'meanings' that could be given to a string of nucleotides.

The sequence of a gene and the sequence of a protein, in conclusion, are not objective properties of those molecules. They are codemaker-dependent properties because they do not exist without a codemaking process and because they would be different if the codemaker had a different structure. The sequences of genes and proteins, in short, have precisely the characteristics that define signs and meanings. They are codemaker-dependent entities made of organic molecules and are, therefore, organic signs and organic meanings. All we need to keep in mind is that *signs and meanings are mental entities when the codemaker is the mind, but they are organic entities when the codemaker is an organic system* (Barbieri 2003a).

We reach in this way the conclusion that every living cell contains all four components of semiosis (signs, meanings, code and codemaker) and is, therefore, a real semiotic system.

Two types of signs

Signs have been divided since antiquity into two great classes that are traditionally represented by *symbols* and *symptoms*. Augustine (389 AD) called them *signa data* and *signa naturalia*, a distinction that continues to these days under the terms of *conventional signs* and *natural signs* (Deely 2006; Favareau 2007). The conventional signs are those where there is no physical relationship between signifiers and meanings, and a connection between them can be established only by arbitrary rules, i.e., by conventions. Words, for example, are signs (because they 'stand for' the named entities) and are conventional signs because they are not determined by the characteristics of the named entities. In the same way, there is no necessary connection between symbols and the entities that they stand for (between a flag and a country, for example).

In natural signs, by contrast, a physical link is always present between signifier and signified. Typical examples are the symptoms that doctors use to diagnose illnesses (spots on the skin, a fever, a swollen area, etc.), as well as a variety of cues (smoke as sign of fire, odors as signs of food, footprints as signs of organisms, etc.). In all these cases, there is a physical relationship between the visible signs and the invisible entities that they point to, and yet the relationship is underdetermined, so much so that it takes a process of learning and an act of interpretation to establish it. The diagnosis of an illness from symptoms, for example, is always an interpretive exercise, and even simple associations, such as those between clouds and rain, depend upon processes of learning and memory.

At the molecular level, we have seen that in protein synthesis, a sequence of nucleotides is used as a sign by a codemaker to produce a sequence of amino acids according to the rules of the genetic code. In that case, there is no necessary connection between the components of the two molecules and the codons of nucleotides are used, therefore, as *conventional* organic signs, i.e., as organic *symbols*.

A sequence of nucleotides, however, can also be used by a copymaker to produce a complementary copy of itself, and in that case, the relationship between the two sequences is no longer established by adaptors but by direct physical interactions between complementary regions. These interactions, however, occur between very small regions of the molecules, and that means that the first sequence provides only a limited number of physical determinants for the second. The first sequence, in other words, does have a physical relationship with the second, but such relationship is undetermined and represents, therefore, only a 'cue', i.e., a *natural* organic sign, for the second.

We conclude that the distinction between natural and conventional signs exists also at the molecular level and represents in fact a divide between two very different types of molecular processes. Sequences of nucleotides are used as natural signs in molecular copying and as conventional signs in molecular coding. The transcription of genes, in other words, is based on natural organic signs, whereas the translation of genes into proteins is based on conventional organic signs.

In both cases, a sequence of nucleotides provides 'information' for the assembly of a second sequence, but the 'meaning' of that information is determined by the molecular machine that actually performs the assembly. Organic information and organic meaning, in short, are not intrinsic properties of the molecules that carry them, and this raises a new problem. What kind of entities are they?

Part 2: the nature of information and meaning

The claim of physicalism

In 1953, Watson and Crick proposed that the linear sequence of nucleotides represents the *information* carried by a gene. A few years later, the mechanism of protein synthesis was discovered, and it was found that the sequence of nucleotides in genes determines the sequence of amino acids in proteins with a process that amounts to a transfer of linear information from genes to proteins. In both types of molecules, therefore, *biological information* was identified with, and defined by, the specific sequence of their subunits.

The concept of biological information threw a completely new light on the century-old mystery of inheritance (*heredity is the transmission of information*) and quickly transformed the whole of biology from an energy-based into an information-based science. It must be underlined,

however, that biological information, or *biological specificity* (as some prefer to call it), cannot be measured and cannot, therefore, be regarded as a physical quantity. So, what is it? A similar problem arises with the genetic code. The rules of a code cannot be measured and a code, therefore, cannot be a combination of physical quantities. So what is it?

According to an influential school of thought, biological information and the genetic code are simply metaphors. They are linguistic constructions that we use in order to avoid long periphrases when we talk about living systems, but no more than that. They are like those computer programs that allow us to write our instructions in English, thus saving us the trouble to write them with the binary digits of the machine language. Ultimately, however, there are only binary digits in the machine language of the computer, and in the same way it is argued that there are only physical quantities at the most fundamental level of Nature.

This conclusion, known as *physicalism*, or *the physicalist thesis*, has been proposed in various ways by a number of scientists and philosophers (Chargaff 1963; Sarkar 1996, 2000; Mahner and Bunge 1997; Griffith and Knight 1998; Griffith 2001; Boniolo 2003). It is probably one of the most deeply dividing issues of modern science. Many biologists are convinced that biological information and the genetic code are real and fundamental components of life, but physicalists insist that they are real only in a very superficial sense, and that there is nothing fundamental about them because they *must* be reducible, in principle, to physical quantities.

It has to be pointed out that the physicalist thesis *could* be true. In fact it would be rigorously true if genes and proteins were made by spontaneous assemblies because these processes are fully described by physical quantities. The point, however, is precisely that genes and proteins are *not* spontaneous molecules. They are molecular artifacts because they are manufactured by molecular machines, and this gives us a real alternative to the physicalist thesis. More precisely, we can prove that physicalism is wrong if we show that it is valid only for spontaneous objects, i.e., if we show that there is a fundamental difference between spontaneous objects and artifacts. To this purpose, we need to go back to our question about biological information and the genetic code.

Information is notoriously a difficult issue, and often biologists tend to identify it with genetic sequences, which are in fact only a particular type of information. A proper introduction to this field is undoubtedly called for, and the reader can find it in qualified publications such as those by Yockey (2005), Battail (2006), and Forsdyke (2006), in addition of course to the classic papers by Shannon (1948). Here, however, we are interested precisely in that particular type of information that is expressed by sequences and in those particular relationships that are the rules of the genetic code. Given that these entities cannot be measured, what exactly are they?

Organic information

In genes and proteins, as we have seen, biological (or organic) information has been defined as the specific sequence of their subunits. This definition, however, is not entirely satisfactory because it gives the impression that information is a *static* property, something that molecules have simply because they have a sequence. In reality, there are countless molecules which have a sequence but only in a few cases this becomes information. That happens only when copymakers use it as a guideline for copying. Even copymakers, however, do not account, by themselves, for information. Copymakers can stick subunits together and produce sequences, but without a template, they would produce only *random* sequences, not specific ones. Sequences alone or copymakers alone, in other words, have nothing to do with information. It is only when a sequence provides a guideline to a copymaker that it becomes information for it. It is only an act of copying, in other words, that brings organic information into existence.

This tells us that organic information is not just the specific sequence of a molecule but *the specific sequence produced by a copying process*. This definition underlines the fact that organic information is not a thing or a property but the result of a process. It is, more precisely, an 'operative' definition because information is defined by the process that brings it into existence. We realize in this way that organic information is as real as the copying process that generates it, but we still do not know what kind of entity it is. How does it fit into our description of Nature?

According to a long tradition, natural entities are divided into *quantities* and *qualities*. Quantities can be measured and are objective, whereas qualities are subjective and cannot be measured. In the case of organic information, however, this scheme breaks down. Organic information is not a quantity because a specific sequence cannot be measured. But it is not a quality either because linear specificity is a feature that we find in organic molecules, and is, therefore, an objective feature of the world not a subjective one.

A scheme based on quantities and qualities alone, in short, is not enough to describe the world. In addition to quantities (*objective and measurable*) and qualities (*subjective and not-measurable*), we must recognize the existence in Nature of a third type of entities (*objective but not-measurable*). Information is one of them, and we can also give it a suitable name. Since we can describe it only by *naming* its sequence, we can say that organic information is a *nominable* entity or that it belongs to the class of the nominable entities of Nature (Barbieri 2003b; 2004).

We conclude that organic information is a new type of natural entity, but we also conclude that it belongs to the same class of objective entities that contains all physical quantities. Therefore, *it has the same scientific 'status' as a physical quantity*. This, however, raises a new problem because there are two distinct classes of physical quantities: a small group of fundamental quantities (space, time, mass, charge, and temperature) and a much larger group of derived quantities. That distinction applies to all objective entities, so we need to understand whether organic information belongs to the first or to the second group.

Luckily, this problem has a straightforward solution because the sequences of genes and proteins have two very special characteristics. One is that *a change in a single component of a biological sequence may produce a sequence which has entirely new properties*. This means that although a biological sequence can be said to have 'components', it is at the same time a single indivisible whole. The second outstanding feature is that *from the knowledge of n elements of a biological sequence we cannot predict the element (n+ 1)*. This is equivalent to saying that *a specific sequence cannot be described by anything simpler than itself*, so it cannot be a derived entity.

We conclude that organic information has the same scientific status as the physical quantities because it is an objective and reproducible entity. But we also conclude that it does not have the status of a derived physical quantity because it cannot be expressed by anything simpler than itself. This means that organic information has the same scientific status as the fundamental physical quantities, i.e., that it is a fundamental (or irreducible) entity of Nature (a similar conclusion was also described in Küppers 1990 and 1992).

Organic meaning

A code is a set of rules, which establish a correspondence between the objects of two independent worlds. The Morse code, for example, is a correspondence between groups of dots and dashes with the letters of the alphabet, and in the same way, the genetic code is a correspondence between groups of nucleotides and amino acids. Let us notice 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 the Morse code, for example, the rule that 'dot–dash' corresponds to letter 'A', is equivalent to saying that letter A is the meaning of dot–dash. In the code of the English language, the mental object of the sound 'apple' is associated to the mental object of the fruit apple, and this is equivalent to saying that that 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. We can say, therefore, that *meaning is an entity which is related to another entity by a code*, and that organic meaning exists whenever an organic code exists (Barbieri 2003a).

The existence of meaning in the organic world may seem strange, at first, but in reality, it is no more strange than the existence of a code because they are the two sides of the same coin. To say that a code establishes a correspondence between two entities is equivalent to saying that one entity is the meaning of the other, so we cannot have codes without meaning or meaning without codes. All we need to keep in mind, once again, is that meaning is a mental entity when the code is between mental objects, but it is an organic entity when the code is between organic molecules.

Modern biology has readily accepted the concept of information but has carefully avoided the concept of meaning, and yet, organic information and organic meaning are both the result of natural processes. Just as it is an act of copying that creates organic information, so it is an act of coding that creates organic meaning. Copying and coding are the processes; copymakers and codemakers are their agents; organic information and organic meaning are their results. But the parallel goes even further. We have seen that organic information cannot be measured, and the same is true for organic meaning. We have seen that organic information is an objective entity because it is defined by the same sequence for any number of observers, and that is also true for organic meaning, which is defined by coding rules that are the same for all observers. Finally, we have seen that organic information is an irreducible entity because it cannot be described by anything simpler than its sequence, and the same is true for organic meaning, which cannot be defined by anything simpler than its coding rules.

Organic information and organic meaning, in short, belong to the same class of entities because they have the same general characteristics: They both are *objective-but-not-measurable* entities, they both are irreducible, or *fundamental*, entities of Nature, and since we can describe them only by naming their components, they both are *nominable* entities (Barbieri 2003b, 2004). Finally, let us underline that they are the twin pillars of life because organic information comes from the copying process that produces genes, while organic meaning comes from the coding process that generates proteins.

Operative definitions

Physical quantities have three fundamental properties: (1) they are objective, (2) they are reproducible, and (3) they are defined by operative procedures. This last property is

particularly important because it has provided the solution to one of the most controversial issues of physics. The controversy was about the theoretical possibility that the entity which is measured may not be the same entity which has been defined. This led to the idea that there should be no difference between what is measured and what is defined, i.e., to the concept of operative (or operational) definition: *a physical quantity is defined by the operations that are carried out in order to measure it*.

It was this operational approach that solved the definition problem in physics, and it is worth noticing that we can easily generalize it. Rather than saying that a natural entity is defined by the operations that measure it, we can say that a *natural entity is defined by the operations that evaluate it in an objective and reproducible way.* The advantage of this generalized formulation is that it applies to *all* objective entities, so it can be used not only in physics but in biology as well. To this purpose, we only need to notice that *a* measurement is an objective and reproducible description of a physical quantity, just as the naming of a specific sequence is an objective and reproducible description of organic information, and just as the naming of a coded entity is an objective and reproducible description of organic meaning.

Whereas the physical quantities are evaluated *by measuring*, sequences and codes are evaluated *by naming their components*, but in both cases the entities in question are defined by the operations that evaluate them, and this is the essence of the operative approach. We may add that organic information and organic meaning can also be defined by the processes of copying and coding that bring them into existence, and that too amounts to an operative definition (Barbieri 2003b, 2004).

We conclude that organic information and organic meaning can be defined by generalized operative procedures that are as reliable as the operative procedures of physics. This means that the definitions of information and meaning should no longer be at the mercy of endless debates on terminology as they have been in the past. The operative definitions are scientific tools which are justified by their own prescriptions, so there is no point in asking whether they are right or wrong. All we can ask of them is whether they contribute or not to our description and to our understanding of Nature.

At this point, we can summarize all the above arguments with the following concepts:

1. The sequence used by a copymaker during a copying process is *organic information*.
2. The sequence used by a codemaker during a coding process is an *organic sign*.
3. The sequence produced by a codemaker during a coding process is an *organic meaning*.
4. Organic information, organic signs, and organic meanings are neither quantities nor qualities. They are a new kind of natural entities, which are referred to as *nominable* entities.
5. Organic information, organic signs, and organic meanings have the same scientific status as physical quantities because they are *objective* and *reproducible* entities that can be defined by operative procedures.
6. Organic information, organic signs, and organic meanings have the same scientific status as *fundamental* physical quantities because they cannot be reduced to, or derived from, simpler entities.

The unexpected properties of artifacts

Sequences, codes, signs and meanings exist only in a world of artifacts because they are brought into existence by copying and coding, the very processes that give origin to artifacts. But can we really say that a set of artifacts is a *world*? Are there regularities and laws in such a world *in addition* to those of physics and chemistry? In order to find this out, let us start from the special case of those particular human artifacts that we call 'numbers'.

There is little doubt that numbers arose by counting, and that counting was favored by natural selection because it had practical advantages. The process of counting, however, produces exclusively natural numbers, but then we have discovered prime numbers, rational and irrational numbers, real and imaginary numbers, and an endless stream of mathematical theorems. All these additional entities were not produced by counting, and this is why some mathematicians say that natural numbers were *invented* by man but that all other rules of mathematics could only be *discovered*, as if they had an existence of their own. In practice, this is equivalent to saying that the world of mathematics was generated by the 'genetic' rule of counting, and then it developed into an increasingly complex world full of additional or 'epigenetic' properties. A world of artifacts, in short, may not be completely described by the coding rules that generate the artifacts. It may well have unexpected *rules of its own*, rules that we may call *epigenetic* because they were not present at the beginning and appeared only during a process of exploration and development.

Can we extend this conclusion to other artifacts? Today, something similar seems to exist also in the world of language, where it has been discovered that children learn to speak by using only a limited number of inputs from the environment. According to Chomsky (1975), this suggests the existence of a universal grammar, a mechanism that has the ability to retrieve the countless rules of any particular language from a limited sample of them. It is as if the brain

of a child 'explores' the world of language and 'discovers' an unlimited number of new rules simply by applying the basic algorithm of the universal grammar.

A parallel conclusion appears to be valid also in the world of proteins. There is a universal mechanism in every cell that produces linear polypeptides from linear sequences of genes, but then the polypeptides fold up into three-dimensional proteins whose forms and behaviors are not written in the genes, and living cells appear to engage in a veritable exploration of the potentialities of the protein world.

Mathematics, language, and proteins are very different sets of artifacts, but deep down, there is something in common between them. They all have (1) a genetic algorithm that starts producing the objects of a potentially unlimited new world of artifacts (numbers, words, or proteins) and (2) an exploratory procedure that brings into existence additional or epigenetic properties of the new world that were not present at the beginning. We conclude, therefore, that many types of artifacts have unexpected properties which can be discovered only by a process of exploration, and in those cases we can truly say that we are in the presence of new explorable worlds. We also conclude that a complete description of a world of artifacts requires new fundamental entities in addition to physical quantities, and that is tantamount to saying that the claim of physicalism does not apply to the living world.

Schrödinger's prophecy

In 1944, Erwin Schrödinger wrote "What is Life?", a little book that inspired generations of scientists and became a landmark in the history of molecular biology. There were two seminal ideas in that book: one was that the genetic material is like an *aperiodic crystal*, the other was that *the chromosomes contain a code-script for the entire organism*.

The metaphor of the aperiodic crystal was used by Schrödinger to convey the idea that the atoms of the genetic material must be arranged in a unique pattern in every individual organism, an idea that later was referred to as *biological specificity*. The metaphor of the code-script was used to express the concept that there must be "a miniature code" in the hereditary substance, a code that Schrödinger compared to "a Morse code with many characters", and that was supposed to carry "the highly complicated plan of development of the entire organism." That was the very first time that the word code was associated to a biological structure and was given a biological function.

The existence of specificity and a code at the heart of life led Schrödinger to a third seminal conclusion, an idea that he expressed in the form of a prophecy: "Living matter, while not eluding the 'laws of physics' as established up to date, is likely to involve hitherto unknown 'other laws of physics', which, however, once they have been revealed, will form just an integral part of this science as the former". Schrödinger regarded this prophecy as his greatest contribution to biology, indeed, he wrote that it was "my only motive for writing this book", and yet that is the one idea that even according to his strongest supporters did not stand up to scrutiny. Some 30 years later, Gunther Stent gave up the struggle and concluded that "No 'other laws of physics' turned up along the way (Stent and Calendar 1978). Instead, the making and breaking of hydrogen bonds seems to be all there is to understanding the workings of the hereditary substance".

Schrödinger's prophecy seems to have been shipwrecked in a sea of hydrogen bonds, but in reality that is true only in a very superficial sense. The essence of the prophecy was about the existence of something fundamentally new, and that turned out to be true. As we have seen, life is based on organic information and organic meaning, and these are indeed new fundamental entities of Nature. Schrödinger invoked the existence of new *laws* rather than of new *entities*, but that was only a minor imperfection and should not have been allowed to obscure the substance of the prophecy.

There is, however, one thing that Schrödinger might not have appreciated in the answer that here has been given to the question "What is Life?". Together with many other physicists, he believed that scientific truths must have *beauty*, and the answer "Life is artifact-making" might not be elegant enough to meet his criterion of truth. Luckily, there is a simple way out of this impasse because the word *artifact-making* maintains its meaning even when we drop all its letters but the first three. In this way, the statement that "Life is artifact-making" becomes "Life is art", and that is a conclusion that even Schrödinger might have approved of.

Part 3: the organic codes

The fingerprints of the organic codes

Codes and conventions are the basis of all cultural phenomena and from time immemorial have divided the world of culture from the world of nature. The rules of grammar, the laws of government, the precepts of religion, the value of money, the cooking recipes, the fairy tales and the rules of chess are all human conventions that are profoundly different from the laws of physics and chemistry, and this has led to the conclusion that there is an unbridgeable gap between nature and culture. Nature is governed by objective immutable laws, whereas culture is produced by the mutable conventions of the human mind.

In this century-old framework, the discovery of the genetic code in the early 1960s came as a bolt from the blue, but strangely enough it did not bring down the barrier between nature and culture. On the contrary, various

'protective belts' were quickly built around the old divide with arguments that effectively emptied the discovery of the genetic code of all its revolutionary potential. The first protective belt was the argument that the genetic code is fundamentally a metaphor because it must be reducible, in principle, to physical quantities. The second protective belt was the idea that the genetic code has been an extraordinary exception, something that happened at the origin of life and was never followed by anything similar ever since.

But are we sure that the genetic code is the only organic code of the living world? Luckily, this is a problem that we can deal with, because if other organic codes exist we should be able to discover them by the standard experimental procedures of science, just as we have discovered the genetic code.

The first step, in this enterprise, is to underline the difference that exists between copying and coding, a difference that is particularly evident in transcription and translation. In transcription, an RNA sequence is assembled from the linear information of a DNA sequence, and in this case a normal biological catalyst (an RNA polymerase) is sufficient because each elementary step requires a single recognition process. In translation, instead, two independent recognition processes must be performed at each step, and the system that performs the reactions (the ribosome) needs special molecules, first called adaptors and then transfer RNAs, in order to associate codons to amino acids according to the rules of the genetic code. Without a code, in fact, a codon could be associated to different amino acids and biological specificity, the most precious of life's properties, would be lost.

These concepts can easily be generalized. We are used to think that biochemical processes are all catalyzed reactions, but in reality we should sharply distinguish between catalyzed and codified reactions. Catalyzed reactions are processes (like transcription) that require only one recognition process at each step, whereas codified reactions require (like translation) two independent recognition processes at each step and a set of coding rules. The catalyzed reactions, in other words, require catalysts, whereas the codified reactions require adaptors, i.e., catalysts plus a code.

Any organic code is a set of rules that establish a correspondence between two independent worlds, and this necessarily requires molecular structures that act like adaptors, i.e., that perform two independent recognition processes. The adaptors are required because the two worlds would no longer be independent if there were a necessary link between them, and a set of rules is required in order to guarantee the specificity of the correspondence. In any organic code, in short, we should find three major features:

1. A correspondence between two independent worlds.
2. A system of molecular adaptors.
3. A set of rules that guarantee biological specificity.

We conclude that the adaptors are the key molecules of the organic codes. They are the molecular fingerprints of the codes, and their presence in a biological process is a sure sign that that process is based on a code. This gives us an objective criterion for the search of organic codes, and their existence in Nature becomes, therefore, first and foremost, an experimental problem.

The splicing codes

One of the greatest surprises of molecular biology was the discovery that the primary transcripts of the genes are often transformed into messenger RNAs by removing some RNA pieces (called *introns*) and by joining together the remaining pieces (the *exons*). The result is a true assembly because exons are assembled into messengers, and we need, therefore, to find out if it is a catalyzed assembly (like transcription) or a codified assembly (like translation). In the first case, the cutting-and-sealing operations, collectively known as *splicing*, would require only a catalyst (comparable to a RNA-polymerase), whereas in the second case they would need a catalyst and a set of adaptors (comparable to ribosome and tRNAs).

This suggests immediately that splicing is a codified process because it is implemented by structures that are very much comparable to those of protein synthesis. The splicing bodies, known as *spliceosomes*, are huge molecular machines like ribosomes and employ small molecular structures, known as *snRNAs* or *snurps*, which are like tRNAs. The similarity, however, goes much deeper than that because the snRNAs have properties that fully qualify them as adaptors. They bring together, in a single molecule, two independent recognition processes, one for the beginning and one for the end of each intron, thus creating a specific correspondence between the world of the primary transcripts and the world of messengers.

The two recognition steps are independent not only because there is a physical distance between them but above all because the first step could be associated with different types of the second one, as demonstrated by the cases of *alternative splicing*. The choice of the beginning and of the end of an intron, furthermore, is the operation that actually defines the introns and gives them a meaning. Without a complete set of such operations, primary transcripts could be transformed arbitrarily into messenger RNAs, and there would be no biological specificity whatsoever.

In RNA splicing, in conclusion, we find the three basic characteristics of all codes: (1) a correspondence between two independent worlds, (2) the presence of molecular adaptors, and (3) a set of rules that guarantee biological specificity. We conclude, therefore, that the processing of RNA transcripts into messengers is truly a codified

process based on adaptors and takes place with rules that can rightly be given the name of *splicing codes* (Barbieri 1998, 2003a).

The signal transduction codes

Living cells react to a wide variety of physical and chemical stimuli from the environment, and in general their reactions consist in the expression of specific genes. We need, therefore, to understand how the environment interacts with the genes, and the turning point, in this field, came from the discovery that the external signals (known as *first messengers*) never reach the genes. They are invariably transformed into a different world of internal signals (called *second messengers*) and only these, or their derivatives, reach the genes. In most cases, the molecules of the external signals do not even enter the cell and are captured by specific receptors of the cell membrane, but even those that do enter (some hormones) must interact with intracellular receptors in order to influence the genes (Sutherland 1972).

The transfer of information from environment to genes takes place, therefore, in two distinct steps: one from first to second messengers, which is called *signal transduction*, and a second path from second messengers to genes, which is known as *signal integration*. The surprising thing about signal transduction is that there are hundreds of first messengers (hormones, growth factors, neurotransmitters, etc.), whereas the known second messengers are only of four types (cyclic AMP or GMP, calcium ions, inositol trisphosphate, and diacylglycerol; Alberts et al. 1994).

First and second messengers, in other words, belong to two very different worlds, and this suggests immediately that signal transduction may be based on organic codes. This is reinforced by the discovery that there is no necessary connection between first and second messengers because it has been proved that the same first messengers can activate different types of second messengers, and that different first messengers can act on the same type of second messengers. The only plausible explanation of these data is that signal transduction is based on organic codes, but of course we would also like a direct proof.

The signature of an organic code, as we have seen, is the presence of adaptors and the molecules of signal transduction do have the defining characteristics of the adaptors. The transduction system consists of at least three types of molecules: a *receptor* for the first messengers, an *amplifier* for the second messengers, and a *mediator* in between (Berridge 1985). The system performs two independent recognition processes, one for the first and the other for the second messenger, and the two steps are connected by the bridge of the mediator. The connection, however, could be implemented in countless different ways since any first messenger can be coupled with any second messenger, and this makes it imperative to have a code in order to guarantee biological specificity.

In signal transduction, in short, we find all the three characteristics of the codes: (1) a correspondence between two independent worlds, (2) a system of adaptors that give meanings to molecular structures, and (3) a collective set of rules that guarantee biological specificity. The effects that external signals have on cells, in conclusion, do not depend on the energy or the information that they carry, but on the *meaning* that cells give them with rules that we can rightly refer to as *signal transduction codes* (Barbieri 1998, 2003a).

The cytoskeleton codes

A cytoskeleton is absolutely essential for typical eukaryotic processes such as phagocytosis, mitosis, meiosis, ameboid movement, organelle assembly, and three-dimensional organization of the cell, i.e., for all those features that make eukaryotic cells so radically different from bacteria. The actual cytoskeleton, in reality, is an integrated system of three different cytoskeletons made of filaments (*microfilaments*, *microtubules*, and *intermediate filaments*), each of which gives a specific contribution to the three-dimensional form of the cell and to its mobility.

The driving force of the cytoskeleton is a very unusual mechanism that biologists have decided to call *dynamic instability*. The cytoskeletal filaments—especially microtubules and microfilaments—are in a state of continuous flux where monomers are added to one end and taken away at the other, and the filament is growing or shortening according to which end is having the fastest run. But what is really most surprising is that all this requires lots of energy, which means that the cell is investing enormous amounts of energy not in building structures but *in making them unstable*!

In order to understand the logic of dynamic instability, we need to keep in mind that cytoskeletal filaments are unstable only when their ends are not attached to special molecules that have the ability to anchor them. Every microtubule, for example, starts from an organizing center (the *centrosome*), and the extremity which is attached to this structure is perfectly stable, whereas the other extremity can grow longer or shorter and becomes stable only when it encounters an anchoring molecule in the cytoplasm. If such an anchor is not found, the whole microtubule is rapidly dismantled and another is launched in another direction, thus allowing the cytoskeleton to explore all cytoplasm's space in a short time.

Dynamic instability, in other words, is a mechanism that allows the cytoskeleton to build structures with an *exploratory strategy*, and the power of this strategy can be evaluated by considering how many different forms it can give rise to. The answer is astonishing: the number of

different structures that cytoskeletons can create is potentially unlimited. It is the anchoring molecules (that strangely enough biologists call *accessory proteins*) that ultimately determine the three-dimensional forms of the cells and the movements that they can perform, and there could be endless varieties of anchoring molecules. The best proof of this enormous versatility is the fact that the cytoskeleton was invented by unicellular eukaryotes but was later exploited by metazoa to build completely new structures such as the axons of neurons, the myofibrils of muscles, the mobile mouths of macrophages, the tentacles of killer lymphocytes, and countless other specializations.

Dynamic instability, in conclusion, is a means of creating an endless stream of cell types with only one common structure and with the choice of a few anchoring molecules. But this is possible only because there is no necessary relationship between the components of the cytoskeleton and the cellular structures that the cytoskeleton is working on. The anchoring molecules (or accessory proteins) are true adaptors that perform two independent recognition processes: microtubules on one side and different cellular structures on the other side. The resulting correspondence is based, therefore, on arbitrary rules, on true natural conventions that we can refer to as *the cytoskeleton codes* (Barbieri 2003a).

The compartment codes

Eukaryotic cells not only produce molecules of countless different types but manage to deliver them to different destinations with astonishing precision, and this gives us the problem of understanding how they manage to cope with such an immensely intricate traffic. The first step in the solution of this mystery came with the discovery that the Golgi apparatus is involved not only in the biochemical modification of many molecules but also in the choice of their geographical destination. But the truly remarkable thing is that all this is achieved with an extremely simple mechanism. More precisely, the Golgi apparatus delivers countless molecules to their destinations with only three types of vesicles. One type has labels for the transport of proteins outside the cell and another for their delivery to the cell interior, whereas the vesicles of the third type carry no destination label and are programmed, *by default*, to reach the plasma membrane. The solution is extraordinarily efficient. With a single mechanism and only two types of labels, the cell delivers a great amount of proteins to their destinations and also manages to continually renew its plasma membrane.

The Golgi apparatus, however, is a transit place only for a fraction of the cell proteins. The synthesis of all eukaryotic proteins begins in the soluble part of the cytoplasm (the *cytosol*) together with that of a signal that specifies their geographical destination. The piece of the amino acid chain that emerges first from the ribosome (the so-called peptide leader) can contain a sequence that the cell interprets as an export signal to the endoplasmic reticulum. If such a signal is present, the ribosome binds itself to the reticulum and delivers the protein into its *lumen*. If not, the synthesis continues on free ribosomes, and the proteins are shed into the cytosol. Of these, however, only a fraction remains there because the amino acid chain can carry, in its interior, one or more signals, which specify other destinations such as the *nucleus*, the *mitochondria*, and other cell compartments. Proteins, in conclusion, carry with them the signals of their geographical destination, and even the absence of such signals has a meaning because it implies that the protein is destined to remain in the cytosol.

The crucial point is that there is no necessary correspondence between protein signals and geographical destinations. The export-to-the-nucleus signals, for example, could have been used for other compartments or could have been totally different. They and all the other geographical signals are purely conventional labels, like the names that we give to streets, to cities, to airports, and to holiday resorts. The existence of eukaryotic compartments, in other words, is based on natural conventions, and to their rules of correspondence, we can legitimately give the name of *compartment codes* (Barbieri 2003a).

A world of codes

In the 1980s and 1990s, Edward Trifonov started a life-long campaign in favor of the idea that the nucleotide sequences of the genomes carry several messages simultaneously and not just the message revealed by the classic triplet code. He concluded that there are many overlapping codes in the genome and gave them the collective name of *sequence codes*. That conclusion rests upon Trifonov's definition that "a code is any sequence pattern that can have a biological function" or "codes are messages carried by sequences" or "a code is any pattern in a sequence which corresponds to one or another specific biological function" (Trifonov 1989, 1996, 1999).

The plurality of codes described by Trifonov is a result of his particular definition but is not necessarily limited by that, and may well be compatible with other approaches. The splicing code, for example, is a code not only according to his criterion but also according to the operative definition that a code is a set of rules of correspondence implemented by adaptors. This suggests that Trifonov's conclusion may have a general validity, and at least some of his sequence codes could well be true organic codes. For the time being, however, let us acknowledge the fact that according to Trifonov's definition, there are at least eight

sequence codes in the genomes of living creatures, in addition to the classic triplet code (Trifonov 1996): (1) the *transcription codes*, (2) the *gene splicing code*, (3) the *translation pausing code*, (4) the *DNA structure code*, or *DNA shape code*, (5) the *chromatin code*, (6) the *translation framing code*, (7) the *modulation code*, and (8) the *genome segmentation code*.

Other authors have adopted different definitions of code, but this is hardly surprising because biologists are used to employing concepts without waiting for their precise definition (there are still many definitions of 'species', for example, but that does not prevent biologists from using the word species in all cases). What really matters is that the experimental evidence suggests the existence of a wide variety of organic codes in Nature whatever is the criterion used for defining them. More precisely, the existence of the following has been reported:

1. The *Adhesive Code* (Readies and Takeichi 1996; Shapiro and Colman 1999)
2. The *Sugar Code* (Gabius 2000; Gabius et al. 2002)
3. The *Histone Code* (Strahl and Allis 2000; Turner 2000, 2002; Gamble and Freedman 2002)
4. The *Neural Transcriptional Codes* (Jessell 2000; Flames et al. 2007)
5. A *Regulatory Code in mammalian organogenesis* (Scully and Rosenfeld 2002)
6. A *Code of Post Translational Modifications* (Khidekel and Hsieh-Wilson 2004)
7. A *Neural Code for written words* (Dehaene et al. 2005)
8. A *Nuclear Receptors Combinatorial Code* (Perissi and Rosenfeld 2005)
9. A *Transcription Factors Code* (Tootle and Rebay 2005)
10. An *Acetylation Code* (Knights et al. 2006)
11. An *Estrogen Receptor Code* (Leader et al. 2006)
12. The *Metabolic Codes* (Bruni 2007)
13. The *RNA Codes* (Faria 2007)
14. The *Error-Correcting Codes* (Battail 2007; Gonzalez 2008)
15. The *Modular Code of the Cytoskeleton* (Gimona 2008)
16. A *Lipid-based Code in nuclear signaling* (Maraldi 2008)
17. The *Immune Self Code* (Neuman 2008)
18. The *Signal Transduction Codes* (Faria 2008)
19. The *Codes of Language* (Cowley 2008)
20. The *Musical Code* (Reybrouck 2008)

These discoveries have largely been seen as proof of the extreme complexity of life, which they certainly are, but they are also much more than that. They may look like those increasingly complex epicycles that people had to invent in order to keep the Ptolemaic system up, but in reality they raise fundamental questions and point to a new Copernican framework for biology. We have already seen that the existence of the genetic code proves that the cell is a semiotic system, and in the following sections, we will see that the existence of many other organic codes brings to light a new mechanism of evolution.

Part 4: the mechanisms of evolution

Molecular change and evolutionary change

The mechanisms of evolution have been one of the most controversial issues in biology and the great debate about them culminated, in the 1930s and 1940s, in the Modern Synthesis, the theoretical framework where natural selection is regarded as virtually the sole mechanism of evolutionary change.

Natural selection is due to chance variations in the transmission of hereditary characters and is based, therefore, on the mechanism of molecular copying because the copying of a gene is the elementary act that leads to heredity. When a process of copying is repeated indefinitely, however, another phenomenon comes into being. Copying mistakes become inevitable, and in a world of limited resources not all changes can be implemented, which means that a process of selection is bound to take place. Molecular copying, in short, leads to heredity, and the indefinite repetition of molecular copying in a world of limited resources leads to *natural selection*. That is how natural selection came into existence. Molecular copying started it and molecular copying has perpetuated it ever since. This means that *natural selection would be the sole mechanism of evolution if molecular copying were the sole basic mechanism of life.*

As a matter of fact, this *could* have happened. If living systems could have been made entirely of RNA enzymes and RNA genes, only the copying of RNA molecules would have been necessary, and natural selection could indeed have been the sole mechanism of evolution. But that is not what happened. Long before the origin of the first cells, proteins were being made on the primitive Earth, and proteins, unlike genes, could not be made by copying.

The discovery of the genetic code has proved that there are *two* distinct molecular mechanisms at the basis of life, transcription and translation, or copying and coding. The discovery of other organic codes, furthermore, allows us to generalize this conclusion because it proves that coding is not limited to protein synthesis. Copying and coding, in other words, are distinct molecular mechanisms, and this suggests that they give origin to two distinct mechanisms of evolution because an evolutionary mechanism is but the long-term result of a molecular mechanism. More precisely, copying leads, in the long run, to natural selection and coding to natural conventions. In order to accept this conclusion, however, we must prove that the two mecha-

nisms are truly different, i.e., that *coding cannot be reduced to copying*. That is, therefore, our challenge. We can prove that natural conventions are a distinct mechanism of evolution only if we prove that copying and coding are two fundamentally different mechanisms of molecular change.

Copying and coding

Copying and coding are both capable of bringing novelties into the world, but they do it in very different ways. By its very nature, the copying mechanism produces either exact copies or slightly different versions of the copied molecules. This means that natural selection produces new objects only by modifying previous ones, i.e., by making objects that are only relatively different from their predecessors. Natural selection, in short, creates *relative* novelties, not absolute ones.

In the case of coding, the situation is totally different. The rules of a code are not dictated by physical necessity, and this means that a new code can establish relationships that have never existed before in the Universe. The objects that are assembled by the rules of a new code can have no relationship whatsoever to previous objects. Natural conventions, in short, create *absolute* novelties, not relative ones.

A second difference between the two mechanisms is that copying operates on *individual* molecules, whereas coding involves a *collective* set of rules. The difference between natural selection and natural conventions, in other words, is the difference that exists between individual change and collective change. An example of this difference can be seen in any language whose evolution is due to variations that take place not only at the level of the individual words but also at the level of the collective rules of grammar.

A third difference between copying and coding is that they involve two different entities. A variation in the copying of a gene changes the linear sequence, i.e., the information of that gene. A variation in a coding rule, instead, changes the meaning of that rule. The great difference that exists between copying and coding, and, therefore, between natural selection and natural conventions, comes from the difference that exists between information and meaning.

There are, in conclusion, three major differences between copying and coding: (1) copying modifies existing objects whereas coding brings new objects into existence, (2) copying acts on individual objects whereas coding acts on collective rules, and (3) copying is about biological information whereas coding is about biological meaning. Copying and coding, in short, are profoundly different mechanisms of molecular change, and this tells us that natural selection and natural conventions are two distinct mechanisms of evolutionary change.

Different mechanisms at different levels

The idea that natural selection can work at different levels of organization (genes, organisms, species) has been at the center of countless debates in evolutionary biology. Less attention has been given to the alternative possibility that at different levels of organization there may be at work different mechanisms of evolution. There is, however, at least one case that gives us a clear example of this alternative. It is the origin of mitochondria in the precursors of the eukaryotic cells.

For a long time, it has been assumed that mitochondria came into being by gradual evolution from within the cell, but then it was found out that they originated by the incorporation of whole cells into other cells by endosymbiosis. Those two types of cell had been in existence for millions of years before the symbiosis event, and all their components had been copied at each generation and had been subject to evolution by natural selection. Their coming together in symbiosis, however, was a process that took place *at the cellular level*. It was the cells acting as whole systems that gave origin to endosymbiosis. Their components had to be 'compatible' with endosymbiosis, but in no way had been selected for that purpose. Endosymbiosis, in short, is a mechanism that exists only at the cellular level, not at the molecular level, and represents, therefore, a distinct mechanism of evolution.

In the case of the organic codes, the situation is somewhat intermediate between the molecular and the cellular level. The genetic code, for example, is at the same time a supramolecular system and a subcellular one. All its molecular components must be inherited and copied individually, and yet a code is necessarily a collective entity. The important point is that coding, like endosymbiosis, does not exist at the molecular level. Coding belongs to the supramolecular level just as endosymbiosis belongs to the cellular level. There is no doubt that copying is absolutely necessary for coding, but the crucial point is that it is not *sufficient* for it because copying is a molecular mechanism whereas coding is a supramolecular one. Coding cannot be reduced to copying because they are fundamentally different mechanisms of molecular change that operate at different levels of organization. We conclude, therefore, that evolution was not produced only by natural selection but *by natural selection and by natural conventions* (Barbieri 1985, 2003a), which in no way is a belittlement of natural selection. It is only an extension of it.

Codes and macroevolution

The role of the organic codes in the history of life can be appreciated by underlining that their origins are closely associated with the great events of macroevolution. Any

time that a new organic code came into being, something totally new appeared in Nature, something that had never existed before.

The origin of the genetic code, for example, made it possible to produce proteins with specific sequences and to pass them on indefinitely to other systems. That gave origin to biological specificity and to heredity, the most fundamental of life's properties. The origin of the genetic code, in short, was also the origin of protein-based life, i.e., of life-as-we-know-it.

Similar considerations apply to the other organic codes. The signal transduction codes, for example, allowed primitive systems to produce their own signals and, therefore, to separate their internal space from the outside environment. That was a precondition for the origin of *individuality*, and in particular for the origin of the cell.

Another great innovation was brought about by the codes of splicing because the appearance of a complete set of splicing rules brought something unprecedented into being. Splicing requires a separation in time between transcription and translation and that was a precondition for their separation in space, i.e., for the origin of the nucleus. The defining feature of the eukaryotes, in other words, was made possible by the origin of the splicing codes.

Many other eukaryotic innovations were brought into existence by other organic codes. The cytoskeleton codes, for example, allowed the cells to build their own scaffoldings, to change their own shapes, and to perform their own movements. The origin of embryos was also associated with organic codes because typical embryonic processes like *cell determination*, *cell adhesion*, *cell migration*, and *cell death* have all the qualifying characteristics of codified phenomena (Barbieri 1998, 2003a).

In the case of embryonic development, furthermore, we have entirely new codes before us. The correspondence is no longer between two types of molecules, like genes and proteins or first and second messengers, but between molecules and *cell-states*. The determination of the body axes, for example, is obtained by a link between molecules and *cell memory*. The body axes are the same in all triploblastic animals, but their molecular determinants are of countless different types, which shows that there is no necessary link between molecules and cell states. This means that the link between molecular determinants and cell states can only be realized by codes that we can refer to as *body pattern codes*.

The major events in the history of life, in short, went hand in hand with the appearance of new organic codes, from the first cells all the way up to multicellular life, and this suggests a very deep link between codes and evolution. It suggests that the great events of macroevolution were made possible by the appearance of new organic codes.

The contribution of the codes

The history of life has been 'punctuated' by the appearance of new organic codes, and it has been deeply shaped by their characteristics. Five of them are particularly important.

1. *Discontinuity.* The evolution of the individual rules of a code can take an extremely long time, but the 'origin' of a new code corresponds to the appearance of a 'complete' set of rules and that is a sudden event. The great evolutionary novelties produced by a new code, therefore, appeared suddenly in the history of life. This is a new explanation of the discontinuities that paleontology has documented, and shows that natural selection and natural conventions had complementary roles. Natural conventions account for the discontinuities of the history of life, whereas natural selection explains the gradual transformations that took place in between.
2. *Invariance*. The genetic code appeared at the beginning of the history of life and has remained substantially the same ever since. The same apply to the deep codes that define prokaryotes and eukaryotes. Once in existence, they have not been changed despite the fact that all the molecular components of a code must be inherited and are subject, therefore, to the chance variations of the copying mechanism and to the long-term results of that mechanism, i.e., to natural selection and to neutral drift. The fact that the deep organic codes have been conserved for billion of years suggests that their conservation is *the* top priority in all living systems. Everything else can be changed except the rules of the basic codes of life. While morphological structures did rise and fall countless times, the 'deep' organic codes have never been removed. This tells us that they truly are *the fundamentals* of life, the invariants that persist while everything else is changing.
3. *Additivity.* A new organic code has never abolished previous codes. The genetic code has not been removed by the signal transduction codes, and neither of them has been supplanted by the splicing codes. A new code has always been added to the previous ones, which shows that new codes do not originate by the transformation of previous codes. Once in existence, organic codes do not tend to change, and the origin of a new code is always the origin of an entirely new set of rules.
4. *Stability.* The genetic code is present in all living creatures, but the other organic codes appeared in increasingly smaller groups. The greater the number of codes, the smaller the number of species, which possess them. This shows that living systems coexist whatever

is the number of their codes. Eukaryotes did not remove prokaryotes, and metazoa did not remove unicellular eukaryotes. Every organic code, in short, represents a stable form of life.

5. *Complexity.* The addition of new organic codes to a living system can rightly be regarded as an *increase of complexity* of that system. The structural complexity of some organisms did diminish in time, as many cases of simplification clearly show, but the complexity of the codes has never been lowered. Even the animals which lost or reduced the greatest number of parts, in order to lead a parasitic life, have conserved all the fundamental codes of animal life. The number of organic codes is, therefore, a new measure of biological complexity, and probably it is more fundamental than all the other parameters which have been proposed so far.

The contribution of natural selection

Life is essentially a *manufacturing* activity based on the molecular mechanisms of copying and coding. This conclusion may appear to give importance only to internal factors, as if the environment had almost no role to play, but that is far from being the case. The concept that life is artifact-making gives at least three major roles to the environment.

To start with, it is the environment that provides the building blocks for the manufacturing activity of the living systems. All components of life come from the environment and eventually go back to it, which means that any living system is totally dependent on its surrounding world.

The second point is that it is the environment that decides whether the structures manufactured by copying and coding are viable or not. Copying and coding have the potential to create an unlimited number of artifacts, but not all of them actually work in the real world. Copying and coding propose, but in the end it is the environment that disposes of their products.

The third point is that the environment is not only the place where living systems exist. It is also the place that living systems tend to become adapted to. We have learned from Darwin that in a world of limited resources, not all organisms can survive, and a process of selection is bound to take place. The survival can be a matter of luck, but in general it is the degree of adaptation to the environment that gives the best chances of success, and this means that organisms tend to become more and more adapted to their environment.

The process of adaptation allows organisms to become increasingly capable to cope with the surrounding world, and, therefore, to reduce the distance that separates them from *reality*. Natural selection can be regarded, therefore, as a process that allows organisms to incorporate increasing amounts of reality into their constitution, even if the gap between internal and external reality can never be abolished.

François Jacob has expressed this concept with admirable clarity: "If the image that a bird gets of the insects it needs to feed its progeny does not reflect at least some aspects of reality, there are no more progeny. If the representation that a monkey builds of the branch it wants to leap to has nothing to do with reality, then there is no more monkey. And if this did not apply to ourselves, we would not be here to discuss this point" (Jacob 1982).

Common Descent

Darwin's greatest contribution to Biology was probably the theory of Common Descent, the idea that "all the organic beings which have ever lived on this Earth may be descended from some one primordial form" (Darwin 1859). In fact, when Dobzhansky (1973) wrote that "Nothing in biology makes sense except in the light of evolution", it was Common Descent that he had in mind. The idea that all creatures of the present are linked to all creatures of the past is indeed the greatest unifying theme in biology, the concept that we use as an Ariadne's thread to reconstruct the history of life.

Common Descent, however, is compatible with different mechanisms of evolution, and in order to find out the truth about it we need to know the actual mechanisms that gave origin to biological objects in the course of time. How did novelties appear in the history of life? Did new objects arise by natural selection alone or by natural selection and by natural conventions?

If evolution took place only by natural selection, we would have to conclude that nothing similar to the genetic code appeared again in the four billion years of life's history. But we know that many other organic codes exist in life, and this means that there have been many other *origins* because any new organic code gives origin to unprecedented structures. We have, therefore, two very different versions of Common Descent before us. Evolution by natural selection alone implies *Common Descent with a Single Origin*, whereas evolution by natural selection and by natural conventions leads to *Common Descent with Multiple Origins* (this is not the old theory that cells originated many times because the multiple origins are referred to codes not to cells).

The idea that natural conventions bring absolute novelties into existence is equivalent to saying that life has not lost its creative power in the course of time. The origin of embryos, the origin of the mind, or the origin of language, for example, do not seem to be less of a novelty than the origin of the cell. The theory of Common Descent with Multiple Origins makes us realize that absolute novelties

appeared not only at the beginning but throughout the entire history of life. And that is not a belittlement of Darwin's theory of Common Descent. It is only an extension of it.

Part 5: biosemiotics today

Code-based biosemiotics

The discovery of the genetic code took place between 1961 and 1966 (Nirenberg and Matthaei 1961; Speyer et al. 1963; Nirenberg et al. 1966; Khorana et al. 1966) and inspired an approach to semiotics that can be referred to as *code-based biosemiotics* because it assumes that coding is the defining feature of semiosis.

The manifesto of this approach was written by George and Muriel Beadle in 1966 with a single simple sentence: "the deciphering of the genetic code has revealed our possession of a language much older than hieroglyphics, a language as old as life itself, a language that is the most living language of all — even if its letters are invisible and its words are buried in the cells of our bodies" (Beadle and Beadle 1966).

In 1974, Marcel Florkin coined the term 'biosemiotics' for the study of this molecular language and gave the names *biosemes* and *biosyntagms* to the basic units of molecular semiosis. He emphasized, however, that meaning does not exist at the molecular level and claimed that the genetic code is a correspondence between structures and functions, not between signs and meanings: "A bioseme carries no 'bedeutung', no 'meaning', because its signifier is a molecular structure and its signified is a biological function" (Florkin 1974). The idea that semiosis can exist without meaning may seem paradoxical, today, and yet Florkin's conclusion was entirely logical because it was the consequence of two basic concepts of modern biology.

One is the idea that the cell is a duality of genotype and phenotype, i.e., a biological computer made of genetic software and protein hardware. The crucial point is that a computer contains codes but is *not* a semiotic system because its codes come from a codemaker, which is outside the system. The second basic concept is the idea that all biological novelties are generated by natural selection, i.e., by an agent, which is outside the cell just as the human mind is outside the computer. But if the cell is a biological computer assembled by natural selection, it is perfectly legitimate to say that it is *not* a semiotic system, and this justifies Florkin's statement that there is no real meaning in it. Ultimately, that leads to the physicalist thesis that there is no real code either at the molecular level, and that molecular semiosis is merely an illusion.

The computer model of the cell, in short, keeps semiosis out of the cell, and this is why the first true model of molecular semiosis was the idea that every cell is a trinity of genotype, phenotype, and ribotype, i.e., the idea that the cell contains an *internal* codemaker (Barbieri 1981, 1985). This was complemented by the idea that coding is not reducible to copying, and, therefore, that natural selection (based on copying) and natural conventions (based on coding) are two distinct mechanisms of evolution (Barbieri 1985, 2003a).

Another important contribution to code-based biosemiotics came from the discovery of an increasing number of organic codes. That development started with the unveiling of the sequence codes by Trifonov (1987, 1989, 1996, 1999) and has grown slowly but steadily ever since (Barbieri 2008).

The 'code based' approach to biosemiotics, in short, is a road that started with the recognition of semiosis at the molecular level and worked its way up by extending the concepts of code and meaning to the higher levels of biological organization. At about the same time, however, there was also another road to biosemiotics that was being developed. A road that went exactly the other way round, i.e., that started at the higher levels and worked its way down towards the lower ones.

Sign-based biosemiotics

The idea that animals have feelings, psychologies, 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 man is a semiotic animal, i.e., that only man makes use of signs. This idea was explicitly challenged for the first time only in 1963, when Thomas 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).

That proposal set Sebeok out on a long search for evidence of semiosis in the various fields of the life sciences, and eventually the hunt paid off. The first decisive clue came from reading, in 1976, the original German edition of *Theoretische Biologie* by von Uexküll (1928). That book convinced Sebeok that von Uexküll had already provided abundant evidence of semiosis in the animal world and had been in fact the unintentional founding father of zoosemiotics. The next crucial development was the extension of semiosis beyond the animal world, a generalization that took place in various stages.

In 1981, Martin Krampen argued that plants engage in vegetable semiosis (phytosemiotics), and in 1988, Sorin Sonea proposed that semiosis goes on even in the bacterial world. Still in 1988, Giorgio Prodi suggested that a primitive form of semiosis exists also in molecules and cells and gave it the name of *protosemiosis* or *natural semiosis* (Prodi 1988). The word 'zoosemiotics' became increasingly inadequate, and in 1991 Sebeok replaced it with biosemiotics, a term proposed by Stepanov in 1971, but which had appeared

for the first time in 1962 when Friedrich Rothschild used it to illustrate a new approach to psychology (Kull 1999).

Sebeok's greatest contribution, however, was probably the silent revolution that he brought about in semiotics itself. Up to the 1960s, semiotics was a deeply divided field, virtually on the edge of anarchy, because it was still split into two major schools, one founded by the Swiss linguist Ferdinand de Saussure (1857–1913) and the other by the American philosopher Charles Sanders Peirce (1839–1914). The main difference between them is that Saussure defined the sign as a dual entity, a combination of *signifier* and *signified* (de Saussure 1916), whereas Peirce insisted that it is a triadic relationship between a *representamen*, an *object*, and an *interpretant* (Peirce 1931–1958). According to Peirce, any act of semiosis cannot involve less than three parties because there must necessarily be a process of *interpretation* between sign and meaning. Sebeok's silent revolution effectively disposed of Saussure and put Peirce squarely at the center of semiosis. The most authoritative treatise of semiotics, published in four volumes between 1997 and 2003 by Roland Posner, Klaus Robering, and Thomas Sebeok, makes it clear that by the 1990s, semiotics had become a largely unitary field, and that semiosis was defined in unmistakably Peircean terms:

> We stipulate that the following is a necessary and sufficient condition for something to be a semiosis: A interprets B as representing C. In this relational characterization of semiosis, A is the Interpretant, B is some object, property, relation, event, or state of affairs, and C is the meaning that A assigns to B. (Posner et al. 1997).

By the 1990s, in short, the Peirce approach to semiotics had become almost universally accepted, and it was taken virtually for granted that the extension of semiosis first to the animal world and then to the entire living world was nothing but the extension of Peirce semiosis to life. Sebeok expressed this concept in no uncertain terms by declaring that: "there can be no semiosis without interpretability" (Sebeok 2001).

The identification of semiosis with Peirce semiosis was also accepted by Jesper Hoffmeyer in *Signs of Meaning in the Universe* (1996), the book where he wrote his manifesto and condensed it in the statement that "the basic unit of life is the sign, not the molecule". There was, therefore, a genuine continuity from Sebeok to Hoffmeyer, and their biosemiotics can rightly be referred to as *sign-based biosemiotics*, or more precisely, as *interpretation-based biosemiotics*.

The role of interpretation

In code-based biosemiotics, semiosis is defined by coding not by interpretation. This is because the rules of the genetic code have been virtually the same in all living systems and in all environments ever since the origin of life, which clearly shows that they do not depend on interpretation. In sign-based biosemiotics, instead, interpretation is a defining feature of semiosis, and there is, therefore, a sharp difference between the two approaches. But is this difference insurmountable? Could we not say, for example, that the codemaker of the cell is also an 'interpreter'? Why should we not generalize the concept of interpretation and say that any act of coding is also an act of interpretation?

In principle, of course, we could, but there is a caveat. If we generalize the concept of interpretation in order to include coding, why do we not go the whole way and generalize it even further? Why do we not say, following Taborsky (1999, 2002), for example, that any function

$$f(x) = y$$

is an act of interpretation, whereby the function '*f*' interprets '*x*' as representing '*y*'? In this way, all physical laws expressed by functions like $f(x)=y$ would be processes of interpretation and, therefore, acts of semiosis.

This point is important because Peirce himself embraced this view and concluded that semiosis exists everywhere in the Universe. We realize in this way that if we extend the concept of interpretation, we end up with a *pansemiotic* view not a biosemiotic one. If we want to keep the biosemiotic idea that semiosis exists only in life, therefore, we must also keep the traditional concept of interpretation, and in this case, we can no longer apply the Peirce model to the cell. This does not mean, of course, that the Peirce model is wrong. It means that it is valid only for those living systems that are capable of interpretation in the traditional sense of the word, i.e., for organisms that have a nervous system.

It is likely that the behavior of the first animals was almost entirely determined by genes, but the number of hard-wired responses could not grow indefinitely, and animals started resorting to processes of learning in order to increase their behavioral repertoire. Learning how to respond to a signal, on the other hand, means learning how to interpret that signal, and this amounts to the construction of a behavioral code whose rules are *context-dependent*. At the same time, learning requires a memory where the results of experience are accumulated, and this means that interpretation is also a *memory-dependent* process. A process of interpretation, in short, is a new type of semiosis that is profoundly different from organic semiosis because it is dependent on learning, memory and context.

Systems capable of interpretation, in turn, evolved in many different ways and eventually a third type of semiosis appeared, a semiosis that was based on symbolic codes shared by all members of a community, i.e., on *language*

(Deacon 1997). The evolution of semiosis was characterized, therefore, by three great innovations: (1) the origin of organic semiosis (the *semiotic threshold*), (2) the origin of interpretation (the *hermeneutic threshold*), and (3) the origin of language (the *symbolic threshold*). It was a process that started at the origin of life with context-free codes and produced codes that were more and more context-dependent. Today, our cultural codes are so heavily dependent on context that we can hardly imagine semiosis without interpretation, and yet they are distinct processes, and we need to keep them apart if we want to understand the origin and the evolution of life.

Five schools and a minimal unity

In addition to code- and to sign-based biosemiotics, there are at least three other schools that have recognized the existence of semiosis in organic life. One is the school founded by Gregory Bateson who described evolution as a cosmic process of learning (Hoffmeyer 2008). Another school is the approach developed within physics by Howard Pattee who proposed, since the 1960s, that there must have been an *epistemic cut* at the origin of life (Pattee 1969, 1972, 2001). The third school was inspired by the philosophy of hermeneutics and was developed in particular by Anton Markoš (2002) who argued that biology can catch the essentials of life only by embracing the approach of the humanities.

There is no space, in this brief review, for these additional themes of biosemiotics, and the interested readers are invited to consult the literature and the historical accounts (Favareau 2007). What is important, here, is to underline not only the existence of different schools of biosemiotics but also the fact that a few small steps towards unification have already been taken.

The first came in 2004 at the fourth Gathering in Biosemiotics organized by Anton Markoš in Prague. Jesper Hoffmeyer, Claus Emmeche, Kalevi Kull, Anton Markoš, and Marcello Barbieri met in a pub and decided that what was uniting them—the introduction of meaning in biology—was far more important than their divisions. Up until then, Barbieri had referred to the science of biological semiosis as *semantic biology*, or *biosemantics*, whereas Markoš had been calling it *biohermeneuthics*, but they accepted to give up their favorite names and to adopt the term *biosemiotics* that Thomas Sebeok had been campaigning for with so much passion and vigor. That is when biosemiotics really came of age. It happened when people decided to work together not because they had the same ideas but because they accepted to put their differences aside in the interest of a greater goal.

Today, the differences still exist, but there is also a 'minimal unity' in the field because there are two basic principles, or postulates, that are accepted by virtually all biosemioticians.

1. The first postulate is the idea that semiosis is unique to life, i.e., that a real divide exists between life and inanimate matter. This sharply differentiates biosemiotics from 'pansemiotics', the doctrine that accepts the existence of semiosis even in the physical world.
2. The second postulate is the idea that semiosis and meaning are *natural* entities. This sharply divides biosemiotics from the doctrine of 'intelligent design' and from all other doctrines that maintain that the origin of life on Earth was necessarily the product of a supernatural agency.

Today, in conclusion, biosemiotics is not yet a unified field from an academic point of view, but it is nonetheless a field that provides a new paradigm for biology. Almost everything remains to be written, but the important point is that the main signposts of the new framework are already in place.

Conclusion

The major conclusion of this review is that biological semiosis is a reality because semiosis is based on codes, and organic codes are experimental realities. An equivalent formulation is that all living creatures are semiotic systems because organic codes exist in all of them. This conclusion is based on a variety of arguments that here have been divided, for convenience, into five parts.

1. In Part 1, we have seen that the cell can be described as a trinity of genotype, phenotype, and ribotype because it is made of three distinct types of informational molecules that have three distinct biological roles. Genotype and phenotype are, respectively, the seats of heredity and metabolism, whereas the ribotype is the system that manufactures proteins on the instructions of genes according to the rules of the genetic code. The crucial point is that the ribotype has the defining features of a codemaker, whereas the sequences of genes and proteins are codemaker-dependent entities and have the defining features of signs and meanings. This shows that the cell is a true semiotic system because it contains all the essential features of such systems, i.e., signs, meanings, and code all produced by the same codemaker.
2. In Part 2, we have faced the claim of physicalism, the conclusion that all natural entities must be reducible to physical quantities. This claim is certainly valid for spontaneous objects because all spontaneous reactions are completely accounted for by physical quantities, but

genes and proteins are *not* spontaneous molecules. They are molecular artifacts that are manufactured by molecular machines by copying and coding. The crucial point, here, is that the production of artifacts requires not only physical quantities but also additional entities like sequences and codes. These entities are as real as physical quantities in the sense that they are equally necessary to the description of biological systems, and this means that in no way can we dismiss them as linguistic metaphors. Physicalism, in short, is not valid in a world of artifacts. It is valid only in a world of spontaneous objects, and it is still popular today only because biology has not yet assimilated the idea that genes and proteins are molecular artifacts, that the whole of life is artifact-making.

3. In Part 3, we have seen that the experimental criterion which has led to the discovery of the genetic code, i.e., the presence of adaptors, allows us to prove the existence of many other organic codes. This makes us realize that the genetic code was only the first of a long list of organic codes, which appeared throughout the history of life. We realize furthermore that the appearance of new organic codes was associated with the great events of macroevolution, which is equivalent to saying that the semiotic processes of coding have been instrumental in shaping the history of life on our planet.
4. In Part 4, we have examined the central claim of the Modern Synthesis, the conclusion that natural selection is the sole mechanism that generates biological novelties. The crucial point here is that natural selection is the long-term result of molecular copying and would be the sole mechanism of evolution if copying were the sole basic mechanism of life. But there are two distinct molecular mechanisms at the basis of life, copying and coding, and both of them have long-term consequences. Copying leads in the long run to natural selection and coding to natural conventions, which means that evolution took place by two distinct mechanisms. Natural selection produces new objects by modifying previous ones, whereas natural conventions bring absolute novelties into existence. Even the evolution of life, in short, was based on semiosis because natural conventions represent a distinct mechanism of evolution.
5. In Part 5, we have seen that biosemiotics has been developed independently by at least five different lines of research. One is the Sebeok–Hoffmeyer approach that is based on Peirce's definition of sign and assumes that interpretation is a fundamental feature of semiosis. The second is the organic-codes line of research where semiosis is based on coding, not on interpretation, and the other three are the approaches developed respectively by Gregory Bateson, Howard Pattee, and Anton Markoš. This makes us realize that biosemiotics is still a developing science where many issues, even important ones, remain to be settled.

All versions of biosemiotics, at any rate, share the idea that semiosis is fundamental to life, i.e., that all living creatures are semiotic systems, and the important point is that we already have enough experimental evidence in favor of that idea. Biosemiotics, in conclusion, is a genuine new paradigm for both biology and semiotics, but its future is unpredictable. It truly is like a new continent whose exploration has just began.

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