Cosmos and History: The Journal of Natural and Social Philosophy, vol. 4, nos. 1-2, 2008

LIFE IS SEMIOSIS
THE BIOSEMIOTIC VIEW OF NATURE

Marcello Barbieri

ABSTRACT: The idea that life is based on signs and codes, i.e., that "Life is semiosis", has been strongly suggested by the discovery of the genetic code, but so far it has made little impact, and is largely regarded as philosophy rather than science. The main reason for this is that there are at least three basic concepts in modern biology that keep semiosis squarely out of organic life. (1) The first is the classical model that describes the cell as a biological computer made of genotype and phenotype. A computer contains codes but is not a semiotic system, and this makes it possible to say that the cell too can have a genetic code without being a semiotic system. (2) The second idea is *physicalism*, the doctrine that everything in life must ultimately be accounted for by physical quantities. This amounts to saying that signs and codes do not exist at the molecular level and are but linguistic metaphors that biologists use simply because they are convenient. (3) The third concept is the idea that all biological novelties have been brought into existence by natural selection, an idea which implies that semiotic processes did not have any creative role in evolution. These arguments have effectively ruled out the existence of semiosis in the organic world, thus depriving the discovery of the genetic code of all its revolutionary potential, but here it will be shown that there are experimental facts against *all* of them. More precisely, it will be shown that the cell is a true semiotic system, and that the genetic code has been the first of a long series of organic codes that have shaped the whole history of life on our planet. Biological semiosis, in other words, is a scientific reality because the organic codes are experimental realities. This paper intends to underline precisely the scientific nature of biosemiotics and argues that the time has come to acknowledge that semiosis not only is a fact of life but is 'the' fact that allowed life to emerge from inanimate matter.

KEYWORDS**:** codes, semiosis, information, meaning, origin of life, macroevolution.

INTRODUCTION

The answers to *"What is Life?"* fall into three main groups. Some deny the very possibility of defining life (the 'negationist' type), some maintain that life can be defined only by a long list of properties (the 'pluralist' type), and others look for a single essential feature that divides life from inanimate matter (the 'monothematic' type). Whatever is our ultimate preference, it is not difficult to see that the third group is, in practice, the most useful to start with. If we take this approach, in fact, we may discover that different monothematic answers are equally plausible, and this could lead us to a pluralistic

conclusion. We may then discover that all pluralistic conclusions leave out something that we feel essential to life, and in that case we may be tempted to join the 'negationist' camp.

The monothematic approach, in short, gives us a sensible starting point, and that's why we are adopting it in this paper. Once we have taken this road, the first thing to do is acknowledging that there are already two great monothematic views in modern biology. They are:

1. the idea that "life is replication" and
2. the idea "life is metabolism" (or, in a slightly different version, that "life is autopoiesis").

These two great ideas have dominated the search for the fundamentals of life ever since the discovery that heredity and metabolism are based, respectively, on genes and proteins. The question "What is Life?" has become virtually equivalent to "What was the origin of Life?", and for a long time it has been assumed that there are only two main answers. Life started either with primordial genes or with primordial proteins, which is equivalent to saying that life is either replication or metabolism.

And yet a third answer does exist. It is the idea that "life is semiosis", i.e., that life is based on signs and codes. This idea has been strongly suggested by the discovery of the genetic code, but it has never been accepted by modern biology because it goes against some of its most basic concepts. Here, however, we want to show that organic codes and organic semiosis are, first and foremost, experimental facts, and we simply cannot ignore them, even if their existence requires a new theoretical framework.. The idea that "life is semiosis" is precisely that – a new paradigm that accounts for the existence of organic codes in the living world and for their contribution to the origin and the evolution of life. In order to illustrate this new view of Nature, the paper has been divided into three parts: (1) Semiosis inside the Cell, (2) Evolution by Copying and Coding, and (3) Three Types of Semiosis.

PART 1: SEMIOSIS INSIDE THE CELL

1-1 Life is artifact-making

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, a "protective belt" was quickly built around the old divide with an argument that effectively emptied the discovery of the genetic code of all its revolutionary potential. The argument is that the genetic code is fundamentally a *metaphor* because it must be reducible, in principle, to physical quantities. It is a secondary structure like those computer programs that allow us to write our instructions in English, thus saving us the trouble to write them in binary digits. Ultimately, however, there are only binary digits in the machine language of the computer, and in the same way, it is argued, there are only physical quantities at the most fundamental level of Nature.

This conclusion, known as *physicalism*, is based on one fact and one assumption. The fact is that all spontaneous reactions are completely accounted for by the laws of physics and chemistry. The assumption is that it was spontaneous reactions that gave origin to the first cells on the primitive Earth. According to physicalism, in short, genes and proteins are spontaneous molecules that evolved into the first cells by spontaneous processes.

This, however, is precisely the point that molecular biology has proved wrong. Genes and proteins are *not* produced by spontaneous processes in living systems. They are produced by molecular machines which physically stick their subunits together in the order provided by *external* templates. They are assembled by molecular robots on the basis of outside instructions, and this makes them as different from ordinary molecules as *artificial* objects are from *natural* ones. Indeed, if we agree that objects are natural when their structure is determined from within and artificial when it is determined from without, then we can truly say that genes and proteins are *artificial molecules*, that they are *artifacts made by molecular machines*. This in turn implies that all biological objects are artifacts, and that the whole of life is *artifact-making*.

Spontaneous genes and spontaneous proteins did appear on the primitive Earth but they did not evolve into the first cells, because spontaneous processes do not have biological specificity. They gave origin to *molecular machines* and it was these machines and their products that evolved into the first cells. The simplest molecular machines we can think of are molecules that can 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. Among the various types of bondmakers, 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*. 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.

Proteins, on the other hand, cannot be made by copying, and yet the information

to make them must 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 one-to-one 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 one-to-one 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 happened. The bridge was provided by molecules called *adaptors* (transfer RNAs) that have two recognition sites: one for a group of three nucleotides (a *codon*) and another for an amino acid. The crucial point is that the two recognition sites are physically separated and chemically independent. There is no deterministic link between codons and amino acids, and a one-to-one correspondence between them could only be the result of conventional rules. Only a real code, in short, could guarantee biological specificity, and this means that the evolution of the translation apparatus had to be coupled with the evolution of the genetic code.

Protein synthesis arose therefore from the integration of two different processes, and the final machine was a *code-and-template-dependent-peptide-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.

1-2 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 50s, 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 physical quantities (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 60s, 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 synthetising 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 the ribosoids can become 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 genes and proteins, 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', i.e., 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.

1-3 The Code Model of semiosis

The discovery of the genetic code threw a completely new light on the cell, but is it enough to conclude that the cell is a semiotic system? The answer clearly depends on the definition of semiosis and in particular on the minimal requirements that allows us to recognize the existence of a semiotic system in Nature.

Semiotics is usually referred to as *the study of signs* 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 signs and meanings, 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 *three* distinct entities: *signs, meanings* and *code*.

Signs, meanings and code, 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 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.

1-4 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. One could object that terms like mental signs and mental objects are a clear case of 'mentalism', and this is no longer the received view, today. The important point, however, is that the conclusion remains valid even if we accept that the mind is but a product of the brain and that sounds and images are just the results of neuron firings. Even in this case, the link between the neuron firings that produce the signs and meanings of a language are 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.

1-5 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 it is 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, 2003).

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.

1-6 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,

odours 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 connections between the components of the two molecules and the sequence of nucleotides is used therefore as a *conventional* organic sign, i.e., as an organic *symbol*.

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 a code but by direct physical interactions between complementary surfaces. 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* 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 replication of genes, in other words, is based on natural organic signs, whereas the synthesis of proteins is based on conventional organic signs.

PART 2: EVOLUTION BY COPYING AND CODING

2-1 The organic codes

According to modern biology, the genetic code is the only organic code that exists in the living world, whereas the world of culture has a virtually unlimited number of codes. We know, furthermore, that the genetic code came into being at the origin of life, whereas the cultural codes arrived almost four billion years later. This appears to suggest that evolution went on for almost the entire history of life on Earth, without producing any other organic code after the first one. According to modern biology, in short, the genetic code was a single extraordinary exception, and if nature has only one exceptional code whereas culture contains an unlimited number of them, the real world of codes is culture and the barrier between the two worlds remains intact.

At a closer inspection, however, we realize that the existence of other organic codes not only cannot be ruled out, but can actually be tested. Any organic code is a set of rules of correspondence between two independent worlds, and this requires molecular

structures that act like *adaptors*, i.e., that perform two independent recognition processes. The adaptors are required because there is no necessary link between the two worlds, and a set of rules is required in order to guarantee the specificity of the correspondence. The adaptors, in short, are necessary in all 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. In splicing and in signal transduction, for example, it has been shown that there are true adaptors at work, and that allows us to conclude that those processes are based on *splicing codes* and on *signal transduction codes* (Barbieri, 1998; 2003). In a similar way, the presence of adaptors has suggested the existence of *cytoskeleton codes* and of *compartment codes* (Barbieri, 2003). Many other organic codes, furthermore, have been discovered by using a variety of theoretical and experimental criteria. Among them:

1. the *Sequence Codes* (Trifonov, 1987, 1989; 1996; 1999),
2. the *Adhesive Code* (Redies and Takeichi, 1996; Shapiro and Colman, 1999),
3. the *Sugar Code* (Gabius, 2000; Gabius et at., 2002),
4. the *Histone Code* (Strahl and Allis, 2000; Turner, 2000; 2002; Gamble and Freedman, 2002),
5. the *Neural Transcriptional Codes* (Jessell, 2000; Flames et al., 2007),
6. a *Regulatory Code in mammalian organogenesis* (Scully and Rosenfeld, 2002)
7. a *Code of Post Translational Modifications* (Khidekel and Hsieh-Wilson, 2004),
8. a *Neural Code for written words* (Dehaene S., Cohen L., Sigman M. and Vinckier F., 2005),
9. a *Nuclear Receptors Combinatorial Code* (Perissi and Rosenfeld, 2005),
10. a *Transcription Factors Code* (Tootle and Rebay, 2005),
11. an *Acetylation Code* (Knights et al. 2006),
12. an *Estrogen Receptor Code* (Leader et al. 2006),
13. the *Metabolic Codes* (Bruni, 2007),
14. the *RNA Codes* (Faria, 2007, 2008),
15. the *Error-Correcting Codes* (Battail, 2006, 2007; Gonzalez, 2008),
16. the *Modular Code of the Cytoskeleton* (Gimona, 2008),
17. a *Lipid-based Code in nuclear signalling* (Maraldi, 2008),
18. the *Immune Self Code* (Neuman, 2008), and

19. the *Musical Code* (Reybrouck, 2008).

The definition of code has been somewhat different from case to case, but this is fairly usual in biology (the concept of species, for example, is still defined in many different ways) and does not prevent us from realizing that the living world is literally teeming with organic codes.

2-2 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 40s, 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, in short, 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 mechanisms 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.

2-3 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.

The role of coding in the history of life can be appreciated by underlining that the origins of new organic codes 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, gave origin to *biological specificity*, the most fundamental of life's properties. The signal transduction codes 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 splicing was a precondition for *the origin of the nucleus*, and therefore for the origin of the eukaryotes (Barbieri, 1998, 2003).

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, 2003).

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 macroevolution. It suggests that *the great events of macroevolution were made possible by the appearance of new organic codes.*

2-4 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, 2003). Which in

no way is a belittlement of natural selection. It is only an extension of it.

2-5 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 Theodosius 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 3: THREE TYPES OF SEMIOSIS

3-1 The concept of Manufacturing Semiosis

The discovery of the genetic code suggested that the cell is a semiotic system, i.e., a system based on signs and codes This concept, however, is still a minority view, and we must face the fact that most biologists do not believe that semiosis exists in the organic world. There are many reasons for this, but three of them are particularly important.

(1) The first is the model that describes the cell as a biological computer, i.e., a

system made of genotype and phenotype where genes provide the software and proteins the 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 it. This makes it legitimate to say that the cell too can have a code without being a semiotic system. All we need is the idea that the genetic code was assembled by natural selection, i.e., by a codemaker that was outside the cell just as the human operator is outside the computer.

(2) The second argument is that semiosis is based on signs, and signs simply do not exist in the cell.

(3) The third argument is that the genetic code is but a set of mapping rules, like the Morse code or the codes of our softwares, which reinforces the idea that the cell is a biological computer and therefore it is not a semiotic system.

These are serious obstacles for the concept of organic semiosis, but they are not insurmountable and we already have valid alternatives to all of them.

(1) The first is the idea that the cell is not a duality of genotype and phenotype but a trinity of genotype, phenotype and ribotype, because the ribonucleoprotein system that houses the genetic code (the ribotype) is inside the cell and has an evolutionary priority over genotype and phenotype. This means that the cell has an *internal* codemaker not an *external* one, and is therefore a triadic system, not a dualistic structure assembled by an external agent.

(2) The existence of signs can be recognized by the fact that they are "agent-dependent" entities, because they exist only when an agent (a codemaker) treats them as signs. This makes us realize that in protein synthesis the codons of a messenger RNA are true signs. If the nucleotides were scanned two by two, the codons would be completely different, which proves that they are not objective properties of the RNAs. Codons are codemaker-dependent entities, and have therefore the qualifying feature that defines all signs.

(3) The idea that the genetic code is but a set of mapping rules, like the Morse code, is still very popular because both codes can be described by a "transformation matrix" or a "conversion table". If we take a closer look, however, we discover that there are very substantial differences between them.

(a) One is the fact that the Morse code is perfectly *reversible*, or *invertible*. It transforms the letters of the alphabet into dots and dashes and, vice versa, dots-and-dashes into letters of the alphabet. The same applies to many other cultural codes, for example to the codes that allow us to translate a text from English to Chinese and from Chinese to English, or to transform written words into sounds and sounds into written words. Nothing of the kind takes place in the cell. The genetic code is absolutely *irreversible*, or *non-invertible*. It is a process that goes from genes to proteins and absolutely *not* viceversa. The reverse transformation is not just avoided, it is physically impossible.

(b) Another difference is that the messages written in Morse are perfectly equivalent to those of the Alphabet world. They carry exactly the same information and are simply a different way of expressing the same reality. The Morse code, in short, transforms a

world of entities into a world of *equivalent* entities. In the case of the genetic code, instead, the situation is totally different. Genes and proteins are not at all equivalent objects, they represent completely different worlds.

We reach in this way two important conclusions: (1) one is that protein synthesis is a semiotic process because it is based on code and signs, (2) the other is that protein synthesis is not just a semiosis, but a *manufacturing semiosis*, i.e., a type of semiosis whose sole purpose is to produce objects that could not come into the world in any other way. For a long time it has been assumed that the function of semiosis is to *interpret* the world, and this is undoubtedly true, but it is not the whole truth. We must acknowledge that there is another type of semiosis whose function is not to interpret the world but to manufacture it, to bring its objects into existence.

3-2 The concept of Associative Semiosis

Protein synthesis is the first example of manufacturing semiosis in the history of life, but not the only one. Another outstanding example if splicing, the process that cuts away RNAs pieces from primary transcripts and assembles the remaining pieces into messenger RNAs. Splicing is closely similar to protein synthesis because the splicing bodies, known as *spliceosomes*, are huge molecular machines like ribosomes, and employ small molecular structures, known as *snRNAs*, which are like tRNAs. The similarity, however, goes much deeper than that, because the snRNAs have properties that fully qualify them as *adaptors*, and the presence of adaptors is the experimental proof that a process is based on codes. Splicing is therefore a semiosis, and more precisely a *manufacturing semiosis*, because it actually brings into existence objects that cannot be produced in any other way.

There are however other types of semiosis that do not have a manufacturing function. Signal transduction, for example, is a semiosis because it creates a correspondence between first and second messengers by means of receptor molecules that have all the defining features of adaptors, but it is not a manufacturing semiosis because the second messengers already exist in the cell and are not manufactured by the transduction process. Signal transduction has the function to create specific associations between first and second messengers and represents therefore a type of semiosis that can be referred to as *associative semiosis*.

Other examples of associative semiosis are revealed by the cytoskeleton codes and by the compartment codes of the eukaryotic cells. In all these cases we recognize the existence of semiosis by the presence of adaptors and we realize that their function is to create specific associations between pre-existing objects, not to bring these objects into existence. The function of associative semiosis is therefore totally different from that of manufacturing semiosis, but it is equally fundamental to life. Manufacturing semiosis is about producing objects, whereas associative semiosis is about organizing them into viable structures.

Proteins, for example, are produced by manufacturing semiosis, but in order to

organize them into supramolecular structures like cell membrane, cytoskeleton and intracellular compartments, we need another type of processes, and the existence of adaptors proves that many of these processes are also based on semiosis. Manufacturing semiosis and associative semiosis, in other words, have very different functions but they are both essential to life and represent therefore complementary processes.

The presence of these two types of semiosis can also be recognized at many other levels of organization. Mental objects, for example, are brought into existence by manufacturing processes, and once in existence they are organized into mental structures by associative processes. Manufacturing semiosis and associative semiosis, in short, have complementary functions at all levels of organizations and must therefore have evolved together again and again in the history of life. One may be tempted to conclude that they are enough, but this is not the case and we have to acknowledge that a third type of semiosis does exist in Nature.

3-3 The concept of Interpretive Semiosis

The organic codes of single cells appeared in the first three billion years of the history of life, during the period of cellular evolution, and were involved either in manufacturing semiosis or in associative semiosis. With the origin of animals, however, a third type of semiosis came into being, a type that will be referred to as *interpretive* semiosis because it became specifically involved in the process of interpretation.

The first animals were probably organisms whose behaviour was almost entirely programmed by genes, but there is a limit to the number of instructions that can be carried in a genome, and that set the stage for the evolution of a new type of behaviour. Since the number of hard-wired responses could not grow indefinitely, 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 is essentially a *context-dependent* process. At the same time, learning requires a memory where the results of experience are accumulated, which means that interpretation is also a *memory-dependent* process. Animals, in short, became increasingly capable of interpreting the world, and this is a process that does not arise automatically from the fixed rules of organic codes. Interpretation is essentially what Peirce called an 'abduction', a process that is neither induction nor deduction, but a 'rule of thumb' way of creating a link between inputs and outputs. Interpretation, in short, is a semiosis because it is a process that gives meaning to signs, but is a new type of semiosis, because it is dependent on learning, memory and context. It is a type that we can call *abductive* or *interpretive semiosis*.

The idea that semiosis is based on interpretation was proposed by Peirce with the model that a sign is always a triadic relationship between a *representamen*, an *object* and an *interpretant*, but it was Thomas Sebeok who turned this model into the central concept of semiotics. In 1963, Sebeok challenged the century old belief that only man makes use of signs and proposed that animals too communicate by signs. He gave the name of

zoosemiotics to the study of animal semiosis and adopted the model of Peirce because it is precisely the animals' ability to interpret the world that proves the existence of semiosis in them.

This concept was later extended beyond the animal world in various stages. In 1981, Martin Krampen argued that plants too engage in semiosis, 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 at the molecular level and called it *protosemiosis*, or *natural semiosis* (Prodi, 1988). The word zoosemiotics became increasingly inadequate and in 1991 Sebeok replaced it officially with 'biosemiotics'.

The extension of semiosis to all living creatures did not ignore the differences between them and it was acknowledged that there are specific types of semiosis in different taxa. Plant semiosis, for example, is distinct from animal semiosis and both of them from the semiosis of fungi, protists and bacteria. Despite the differences, however, they are all semiotic processes, and allow us to the conclude that semiosis exists in all living systems. This is the essence of biosemiotics and all biosemioticians accept it, but Sebeok's proposal was not limited to that. He insisted that what all living systems have in common is not just semiosis but *interpretive* semiosis. This amounts to saying that the Peirce model applies not only to animals but to all living creatures, i.e., that all types of semiosis are based on interpretation. Sebeok expressed this concept in no uncertain terms by declaring that: *"there can be no semiosis without interpretability"* (Sebeok, 2001). This conclusion was also formally expressed in an a treatise that defined semiosis in unmistakably Peircean terms, i.e., in terms of interpretation:

> We stipulate that the following is a necessary and sufficient condition for something to be a semiosis: A interprets B as representing C (Posner et al., 1997).

By the 1990s, in short, the Peirce model of semiosis had become almost universally accepted, and it was taken virtually for granted that all types of semiosis are based on interpretation.

3-4 Three types of semiosis

The Peirce model is undoubtedly valid for animals, but its extension to other living creatures is much more problematic and we definitely cannot apply it to the cell. This is because the rules of the genetic code have been virtually the same in all living systems ever since the origin of life, which clearly shows that they do not depend on interpretation.

The concept of semiosis on the other hand, can de defined without any reference to interpretation because there is no necessary link between them. It can be defined exclusively in terms of coding, and in this form it is immediately applicable to the cell. According to the 'code model', a semiotic system is made of signs, meanings and coding rules, all produced by the same codemaker. In the case of the cell, the translation apparatus is the codemaker, i.e., the seat of the genetic code, the transfer-RNAs are the adaptors that implement the rules of the code, and the sequences of codons and amino

acids have the defining features of signs and meanings because they are codemaker-dependent entities. This tells us that the cell is indeed a semiotic system, but its semiosis is based on coding, not on interpretation.

It may be pointed out that the traditional concept of interpretation could be 'generalized' when we extend it from animals to other living creatures. Couldn't we say, for example, that an act of coding is also an act of interpretation? In principle, of course, we could, but there would be a price to pay, and there are at least two consequences that should warn us against it.

(1) If we generalize the concept of interpretation in order to include coding in it, we end up with a concept that is applicable virtually to everything. Edwina Taborsky, for example, has concluded 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 (Taborsky, 1999, 2000). The important point is that Peirce himself took such a view and concluded that semiosis exists everywhere in the Universe. We realize in this way that a generalized concept of interpretation would give us a *pansemiotic* view of Nature, not a biosemiotic one. If we want to keep the biosemiotic idea that semiosis is unique to life, therefore, we must also keep the traditional concept of interpretation and in this case we can no longer apply it to the cell.

(2) The idea that semiosis is based on interpretation not only in animals but in all living creatures, implies that semiosis is always an 'interpretive' process, that semiosis is exclusively a means of interpreting the world, and this is a very severe limitation, because it means life would get only a partial contribution from semiosis. Life is essentially about three things: (1) it is about manufacturing objects, (2) it is about organizing objects into functioning structures, and (3) it is about interpreting the world. The idea that these are all semiotic processes, tells us that life depends on semiosis much more deeply and extensively than we thought. We realize that there are three distinct types of semiosis in Nature and that interpretive semiosis is only one of them. It is about time therefore that we come to terms with the existence of manufacturing semiosis and associative semiosis in all forms of life, and realize that they actually are the preconditions for the origin of interpretive semiosis in animal life.

CONCLUSION

The greatest problem of biology is understanding the divide that exists between life and matter. There seems to be an unbridgeable gulf between them, but how could life have emerged from matter if it is fundamentally different from it? The received view, today, is that life is but an extremely complex form of chemistry, which is equivalent to saying that there is no fundamental divide between them. Primordial genes and primordial proteins appeared spontaneously on the primitive Earth and gradually evolved into

increasingly more complex structures, all the way up to the first cells. The problem of which molecules came first has been the object of countless debates, but in a way it is a secondary issue. What really matters is that spontaneous genes and spontaneous proteins had the potential to evolve into the first cells. This however, is precisely what molecular biology does not support.

The genes and proteins of the first cells had to have biological specificity, and specific molecules cannot be formed spontaneously. They can only be manufactured by molecular machines, and their production requires entities like sequences and codes that simply do not exist in spontaneous processes. That is what really divides matter from life. All components of matter arise by spontaneous processes that do not require sequences and codes, whereas all components of life arise by manufacturing processes that do require these entities. It is sequences and codes that make the difference between life and matter. It is semiosis that does not exist in the inanimate world, and that is why biology is not a complex form of chemistry

The problem of the origin of life becomes in this way the problem of understanding how the first molecular machines came into existence and started producing new types of molecules. We have seen that chemical evolution could spontaneously produce 'bondmakers', molecules that had the ability to stick subunits together, and we have also seen that some bondmakers could become 'copymakers' by sticking subunits together in the order provided by a template. The next step was the appearance of 'codemakers', and that is much more difficult to account for, but in principle it has the same logic and we can regard it as a natural event (ribosomes, for example, can still arise by self assembly from their components). What really matters is that molecular machines could arise spontaneously, and once in existence they started producing molecules that cannot be formed spontaneously. More precisely, they started producing specific genes and specific proteins and that is what crossed the gulf that divides inanimate matter from life.

The genetic code was the first organic code in the history of life, but was not the only one. We have seen that other organic codes came into existence, and that they account not only for the production of new biological objects but also for the organization of these objects into higher structures and for their interactions with the external world. Semiosis, in short, was not limited to the production of specific molecules. There are at least three different types of semiosis in Nature and we find codes at all levels of life, from the world of genes and proteins all the way up to mind and language. Physics and chemistry provide of course the building blocks of life, but what 'animates' matter is codes, and that is why there is a deep truth in the oversimplified statement that "life is semiosis".

Marcello Barbieri
Department of Morphology and Embryology
Via Fossato di Mortara 64, 44100 Ferrara, Italy
brr@unife.it

BIBLIOGRAPHY

Augustine of Hippo (389ad) *De Doctrina Christiana*. In: Green WM (ed) *Sancti Augustini Opera*, 1963, CSEL 80, Vienna

Barbieri M (1981) The Ribotype Theory on the Origin of Life. *Journal of Theoretical Biology*, 91, 545-601

Barbieri M (1985) *The Semantic Theory of Evolution*. Harwood Academic Publishers, London & New York

Barbieri M (1998) The Organic Codes. The basic mechanism of macroevolution. *Rivista di Biologia-Biology Forum* 91: 481-514

Barbieri M (2003) *The Organic Codes. An Introduction to Semantic Biology*. Cambridge University Press, Cambridge, UK

Barbieri M (2008) *The Codes of Life. The Rules of Macroevolution*. Springer, Dordrecht

Battail G (2006) Should genetics get an information-theoretic education? *IEEE Engineering in Medicine and Biology Magazine*, 25 (1): 34-45

Battail G (2007) Information Theory and Error-Correcting Codes in Genetics and Biological Evolution. In: Barbieri M (ed) *Introduction to Biosemiotics*. Springer, Dordrecht, pp 299-345

Bruni LE (2007) Cellular Semiotics and Signal Transduction. In: Barbieri M (ed) *Introduction to Biosemiotics*. Springer, Dordrecht, pp 365-407

Darwin C (1859) On the Origin of Species by Means of Natural Selection. Murray, London

Deely J (2006) On 'semiotics' as naming the doctrine of signs. *Semiotica* 158: 1-33

Dehaene S, Cohen L, Sigman M, Vinckier F (2005) The neural code for written words: a proposal. *TRENDS in Cognitive Sciences* 9: 335-341

Dobzhansky T (1973) Nothing in biology makes sense except in the light of evolution. *American Biology Teacher* 35: 125-129

Faria M (2007) RNA as Code Makers: A Biosemiotic view of RNAi and Cell Immunity. In: Barbieri M (ed) *Introduction to Biosemiotics*. Springer, Dordrecht, pp 347-364

Faria M (2008) Signal Transduction Codes and Cell Fate. In: Barbieri M (ed) *The Codes of Life: The Rules of Macroevolution*. Springer, Dordrecht, pp 265-283

Favareau D (2007) The Evolutionary History of Biosemiotics. In: Barbieri M (ed) *Introduction to Biosemiotics*. Springer, Dordrecht, pp 1-67

Flames N, Pla R, Gelman DM, Rubenstein JLR, Puelles L, Marin O (2007) Delineation of Multiple Subpallial Progenitor Domains by the Combinatorial Expression of Transcriptional Codes. *The Journal of Neuroscience* 27(36): 9682-9695

Gabius H-J (2000) Biological Information Transfer Beyond the Genetic Code: The Sugar Code. *Naturwissenschaften*, 87: 108-121

Gabius H-J, André S, Kaltner H, Siebert H-C (2002) The sugar code: functional lectinomics. *Biochimica et Biophysica Acta*, 1572: 165-177

Gamble MJ, Freedman LP (2002) A coactivator code for transcription. *TRENDS in Biochemical Sciences*, 27 (4): 165-167

Gimona M (2008) Protein Linguistics and the Modular Code of the Cytoskeleton. In: Barbieri M (ed) *The Codes of Life: The Rules of Macroevolution*. Springer, Dordrecht, pp 189-206

Gonzalez (2008) Error Detection and Correction Codes. In: Barbieri M (ed) *The Codes of Life: The Rules of Macroevolution*. Springer, Dordrecht, pp 379-394

Jessell TM (2000) Neuronal Specification in the Spinal Cord: Inductive Signals and Transcriptional Codes. *Nature Genetics* 1: 20-29

Johannsen W (1909) *Elemente der exacten Erblichkeitslehre*. Gustav Fischer, Jena

Khidekel N, Hsieh-Wilson LC (2004) A 'molecular switchboard'–covalent modifications to proteins and their impact on transcription. *Org. Biomol. Chem.*2:1-7

Knights CD, Catania J, Di Giovanni S, Muratoglu S et al (2006) Distinct p53 acetylation cassettes differentially influence gene-expression patterns and cell fate. *Journal of Cell Biology* 173: 553-544

Krampen M (1981) Phytosemiotics. *Semiotica*, 36 (3/4): 187-209

Leader JE, Wang C, Popov V, Fu M, Pestell RG (2006) Epigenetics and the Estrogen Receptor. *Annals of the New York Academy of Sciences* 1089: 73-87

Maraldi NM (2008) A Lipid-based Code in Nuclear Signalling. In: Barbieri M (ed) *The Codes of Life: The Rules of Macroevolution*. Springer, Dordrecht, pp 207-221

Maynard Smith J, Szathmáry E (1995) *The Major Transitions in Evolution*. Oxford University Press, Oxford.

Neuman Y (2008) The Immune Self Code: From Correspondence to Complexity. In: Barbieri M (ed) *The Codes of Life: The Rules of Macroevolution*. Springer, Dordrecht, pp 247-263

Peirce Charles S (1931-1958) *Collected papers of Charles Sanders Peirce*. Harvard University Press, Cambridge Massachusetts

Perissi V, Rosenfeld MG (2005) Controlling Nuclear Receptors: The Circular Logic of Cofactor Cycles. *Nature Molecular Cell Biology* 6: 542-554

Posner R, Robering K, Sebeok TA (1997) *Semiotik/Semiotics: A Handbook on the Sign-Theoretical Foundations of Nature and Culture* Volume 1. Walter de Gruyter, Berlin, p 4

Prodi G (1988) Material bases of signification. *Semiotica* 69 (3/4): 191-241

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

Reybrouck M (2008) The Musical Code between Nature and Nurture. In: Barbieri M (ed) *The Codes of Life: The Rules of Macroevolution*. Springer, Dordrecht, pp 395-434

Scully KM, Rosenfeld MG (2002) Pituitary Development: Regulatory Codes in Mammalian Organogenesis. *Science* 295: 2231-2235

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

Sebeok TA (2001) Biosemiotics: Its roots, proliferation, and prospects. In: Kull K (ed) Jakob von Uexküll: A Paradigm for Biology and Semiotics. *Semiotica*, 134 (1/4), pp 61-78

Shapiro L, Colman DR (1999) The Diversity of Cadherins and Implications for a Synaptic Adhesive Code in the CNS. *Neuron* 23: 427-430

Sonea S (1988) The global organism: A new view of bacteria. *The Sciences*, 28 (4), 38-45.

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

Taborsky E (1999) Semiosis: the transformation of energy into information. *Semiotica*, 127: 599-646

Taborsky E (2002) Energy and evolutionary semiosis. *Sign Systems Studies*, 30 (1): 361-381

Tootle TL, Rebay I (2005) Post-translational modifications influence transcription factor activity: a view from the ETS superfamily. *BioEssays* 27: 285-298

Trifonov EN (1987) Translation framing code and frame-monitoring mechanism as suggested by the analysis of mRNA and 16s rRNA nucleotide sequence. *Journal of Molecular Biology*, 194: 643-652

Trifonov EN (1989) The multiple codes of nucleotide sequences. *Bulletin of Mathematical Biology*, 51: 417-432

Trifonov EN (1996) Interfering contexts of regulatory sequence elements. *Cabios*, 12: 423-429

Trifonov EN (1999) Elucidating Sequence Codes: Three Codes for Evolution. *Annals of the New York Academy of Sciences*, 870: 330-338

Turner BM (2000) Histone acetylation and an epigenetic code. *BioEssay*, 22: 836-845

Turner BM (2002) Cellular memory and the Histone Code. *Cell*, 111: 285-291

Woese CR (2000) Interpreting the universal phylogenetic tree. *Proceedings of the National Academy of Science USA*, 97: 8392-8396.