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ORIGINAL ARTICLE

Code Biology, Peircean Biosemiotics, and Rosen's Relational Biology

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Abstract

The classical theories of the genetic code (the *stereochemical theory* and the *coevolution theory*) claimed that its coding rules were determined by chemistry—either by stereochemical affinities or by metabolic reactions—but the experimental evidence has revealed a totally different reality: it has shown that any codon can be associated with any amino acid, thus proving that there is no necessary link between them. The rules of the genetic code, in other words, obey the laws of physics and chemistry but are not determined by them. They are *arbitrary*, or *conventional*, rules. The result is that the genetic code is not a *metaphorical entity*, as implied by the classical theories, but a *real code*, because it is precisely the presence of arbitrary rules that divides a code from all other natural processes. In the past 20 years, furthermore, various independent discoveries have shown that many other organic codes exist in living systems, which means that the genetic code has not been an isolated case in the history of life. These experimental facts have one outstanding theoretical implication: they imply that in addition to the concept of *information* we must introduce in biology the concept of *meaning*, because we cannot have codes without meaning or meaning without codes. The problem is that at present we have two different theoretical frameworks for that purpose: one is *Code Biology*, where meaning is the result of coding, and the other is *Peircean biosemiotics*, where meaning is the result of interpretation. Recently, however, a third party has entered the scene, and it has been proposed that Robert Rosen's *relational biology* can provide a bridge between Code Biology and Peircean biosemiotics.

Keywords Biosemiotics · Code Biology · Information · Interpretation · Meaning · Organic codes · Peirce · Relational biology · Rosen

The Organic Codes

A code is a set of rules that establish a correspondence between the objects of two independent worlds, or a mapping between signs and meanings. Saying that there is a code between object 1 and object 2 is equivalent to saying that object 1 is the sign of object 2, or that object 2 is the meaning of object 1. In Morse code, for example, the rule that "dot-dash" corresponds to the letter "A", is equivalent to saying that the letter "A" is the meaning of "dot-dash." Meaning, in other words, is the inevitable product of a code. All we need to keep in mind 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 (Barbieri 2003).

In the case of the genetic code, the rule that a group of three nucleotides (a codon) codes for an amino acid is equivalent to saying that that amino acid is the *organic meaning* of that codon, but this of course is true only if the genetic code is as arbitrary as the Morse code. The key point, in other words, is the *arbitrariness* of the coding rules.

In *Life Itself* (1981) Francis Crick wrote that,

> the genetic code is as important for biology as Mendeleev's Periodic Table of the Elements is for chemistry, but there is an important difference. The Periodic Table would be the same everywhere in the universe. The genetic code appears rather arbitrary, or at least partly so .... If this appearance of arbitrariness in the genetic code is sustained, we can only conclude that all life on earth arose from one very primitive population. (Crick 1981, pp. 46–47)

A few years later that "appearance of arbitrariness" became a certainty because it was shown that any codon can be associated with any amino acid (Schimmel 1987; Schimmel et al.

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1993). Hou and Schimmel (1988), for example, introduced two extra nucleotides in a transfer RNA (tRNA) and found that the resulting tRNA was carrying a different amino acid. Similar results have been obtained by many other modifications of the genetic code (Budisa 2004, 2014; Hartman et al. 2007; Ling et al. 2015), thus proving that there are countless possible connections between codons and amino acids.

Any organic code creates a mapping between two independent worlds of organic molecules and is physically implemented by a third type of molecule, called *adaptors*. In the case of the genetic code the adaptors are the tRNAs, but adaptors are necessarily present in all organic codes, because it is they that provide the links between the two worlds. The adaptors, in short, 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 discovery of the organic codes, and their existence in nature is no longer a matter of speculation. It is, first and foremost, an experimental problem.

Signal transduction, for example, creates a link between first and second messengers, and these molecules belong to two independent worlds because it has been shown that any first messenger could be associated with any second messenger (Alberts et al. 2007). The *transmembrane proteins* of signal transduction, on the other hand, have precisely the function of adaptors, and this reveals the existence of *signal transduction codes* (Barbieri 2003).

In addition to the genetic code and the signal transduction codes, many other codes have been discovered in living systems. Among them, the *metabolic code* (Tomkins 1975), the *sequence codes* (Trifonov 1989, 1996, 1999), the *histone code* (Strahl and Allis 2000; Turner 2000, 2002, 2007; Kühn and Hofmeyr 2014), the *sugar code* (Gabius 2000, 2009), the *splicing codes* (Barbieri 2003; Fu 2004; Buratti et al. 2006; Wang and Burge 2008; Tazi et al. 2009), the *compartment codes* (Barbieri 2003), the *cytoskeleton code* (Barbieri 2003; Gimona 2008), the *tubulin code* (Verhey and Gaertig 2007; Janke 2014), the *nuclear signaling code* (Maraldi 2008), the *injective organic codes* (De Beule et al. 2011; De Beule 2014), the *molecular codes* (Görlich et al. 2011; Görlich and Dittrich 2013), the *ubiquitin code* (Komander and Rape 2012), the *bioelectric code* (Tseng and Levin 2013; Levin 2014), the *acoustic codes* (Farina and Pieretti 2014), and the *glycomic code* (Buckeridge and De Souza 2014).

Organic codes, in conclusion, are an experimental reality, and biology must provide a theoretical framework that accounts for their existence.

The Birth of Code Biology

In March 2001 I sent to Thomas Sebeok the first version of *The Organic Codes*, a manuscript where I pointed out that the existence of the many organic codes in living systems requires that we introduce in biology not only the concept of *information*, but also the concept of *meaning*.

Sebeok kindly acknowledged the manuscript and two months later invited me to review a special issue of *Semiotica* entitled *Jakob von Uexküll: A Paradigm for Biology and Semiotics* (Kull 2001). I accepted, but shortly afterwards I became aware of a sharp contrast between our positions. In my book I had stressed that organic meaning comes from coding, whereas all contributors to the special issue were endorsing the Peircean view that meaning is always produced by a process of interpretation. Another point of contrast was the fact that the contributors advocated a nonmechanistic approach, and biosemiotics was portrayed as the crowning achievement of the idealistic tradition that goes back to Goethe, von Baer, Driesch, and von Uexküll. I argued instead that organic codes and organic meanings are scientific issues that should be investigated with the standard method of science, i.e., with the mechanistic approach of model building. That is why I concluded that the endorsement of nonmechanism was in my opinion a serious mistake for the young field of biosemiotics, the one drawback that could prevent it from growing into a true science.

I reported back to Sebeok that I could not share the majority view in the special issue and would not be surprised if he turned my review down. Surprisingly, however, Sebeok accepted it, and the review appeared in *Semiotica* in the following year (Barbieri 2002). Personally, I took that as a sign that I could argue in favor of a mechanistic approach *from within* the biosemiotic community and decided to join in the *Gatherings in Biosemiotics* meetings. Soon however I realized that our discussions were not enough, that we needed to reach out to a larger audience, and that is why I proposed to create a journal of biosemiotics.

The agreement to do so was reached in June 2004, at the fourth Gathering organized by Anton Markoš in Prague. Jesper Hoffmeyer, Claus Emmeche, Kalevi Kull, Anton Markoš, and I met in a pub and decided that what was uniting us—the introduction of meaning in biology—was far more important than our divisions. Up until then, I had been referring to the study of biological meaning as *semantic biology*, whereas Markoš was calling it *biohermeneutics*, but we agreed to give up those favorite names of ours and to adopt the term *biosemiotics* that Sebeok had been campaigning for with so much passion and vigor.

That is how I came to be the founder and first editor-in-chief of the Springer journal *Biosemiotics*, and although I campaigned for a mechanist approach to meaning I made sure that all schools of biosemiotics were equally represented in the journal, in the hope that in the course of time they would converge toward an increasingly scientific enterprise.

But that, unfortunately, did *not* happen. The number of biosemioticians that endorsed a nonmechanistic view steadily increased, and biosemiotics became increasingly identified with the idea that the cell is capable of interpretation, in line with the Peircean concept that there is an "extended mind" in the universe.

It became painfully clear to me that a scientific approach to meaning could not survive in that framework, and this is why, at the end of 2012, I resigned as editor-in-chief of *Biosemiotics* and together with eleven colleagues founded the new research field of *Code Biology*, a field that was explicitly defined in the constitution of our society as "the study of all codes of life *with the standard methods of science*."

To sum up, there have been two key issues at the origin of Code Biology—the issue of "mechanism" and the issue of "interpretation"—and it is precisely these issues that have been the object of a recent critique of Code Biology. Before examining that critique, therefore, let us take a closer look at those two crucial issues.

The Issue of Mechanism

Ever since the scientific revolution, physics has been at the center of science, and biologists have split into two camps, one in favor and one against adopting the paradigm that has become known as *mechanism*. This paradigm, however, has undergone at least *three major changes* in the last few centuries, and we need to keep them well in mind if we want to avoid misunderstandings.

The first version of mechanism in biology was the Cartesian doctrine that "the body is a machine" and that the clock is its model: "A healthy man is like a well functioning clock," wrote Descartes, "and an ill man is like a clock that needs repairing."

In the course of the next two centuries, this view gradually changed in parallel with the development of chemistry and physics, a change that produced the second version of mechanism: the idea that organisms are *chemical machines* that must be continuously active in order to obey the laws of thermodynamics.

At the beginning of the 20th century the model changed again, and the organism became a duality of genotype and phenotype, in a way similar to the duality of software and hardware in the computer. This was the third version of mechanism in biology: the idea that living systems are *information-processing machines*.

In view of these transformations, we need to ask ourselves: *what actually is mechanism?*

One of the expressions that best catches the spirit of mechanism is John Maynard Smith's statement that, "We understand biological phenomena only when we have invented machines with similar properties" (Maynard Smith 1986, p. 99).

In fact, "understanding" something means describing it in terms that we are familiar with, and a machine gives us an immediate sense of familiarity. When we see it working before our eyes, we feel that we "know" it. Actually, we do not even need to build a machine to get this feeling. A description is enough, and so a machine is often a *model*. One of the most famous machines of all times was built by Turing with just pencil and paper.

A model, furthermore, does not necessarily have a mathematical form. Natural selection, for example, is a mechanistic model that is entirely expressed in words. The important point is that the model has the *logic* of a machine (i.e., that it delivers the same sense of familiarity that we get from a real functioning machine). Mechanism, in short, is the view that scientific knowledge is obtained by building models of what we observe in nature. Let us briefly summarize it.

(1) Mechanism is not reductionism, because a machine is a machine not when it is reduced to pieces but when it is put together into a working whole.
(2) Mechanism is not Newtonian determinism, because it is more general than classical physics (quantum theory is mechanism, and so is nonequilibrium thermodynamics, chaos theory, and the like).
(3) Mechanism is not physicalism, because it is not limited to physical quantities (natural selection, the Turing machine, and Gödel's theorem are mechanistic models that are not based on physical quantities).
(4) Finally, and most importantly, mechanism is made of models, and models do not coincide with reality ("the map is not the territory"), which means that mechanism is intrinsically incomplete and continuously evolving.

Mechanism, in short, is virtually equivalent to the scientific method. The difference between them is that the *hypotheses* of the scientific method are replaced by *models*, i.e., by descriptions of fully functional working systems. Mechanism, in other words, is *scientific modeling*, in the sense that a mechanism is described by a model, and a model is implemented by a mechanism.

Ever since its first appearance, at the beginning of the scientific revolution, mechanism has been highly effective in accounting for particular aspects of nature, and at the same time it has shown an extraordinary ability to change. The first mechanistic model of the body was the clock-machine, then came the steam-engine-machine, and after that the computer-machine. That amounts to saying that mechanism has introduced in biology first *mechanical energy*, then *chemical energy*, and finally *information*.

Now we face the challenge of introducing in biology the last frontier, the concept of *meaning*, and once again we hear that mechanism is not enough, that we need something completely different. Which may be true, of course, but mechanism remains our best chance of finding out what makes living systems tick.

Interpretation at the Brain Level

Charles Sanders Peirce (1839–1914) was an American polymath, educated in chemistry, who made lasting contributions in philosophy, logic, and semiotics: (1) In philosophy he was one of the founders of *pragmatism* (or *pragmaticism* as he called it). (2) In logic he was the first to go beyond Aristotle by adding the new category of *abduction* to the classical Aristotelian categories of *induction* and *deduction* (abduction is an "extrapolation from limited data," an operation where a result is reached by "jumping to conclusions"). (3) In semiotics he built the *doctrine of signs*, a field that he virtually rescued from oblivion after centuries of neglect, and proposed that signs always come from processes of interpretation.

The Peircean concepts of "abduction" and "interpretation" are particularly important in biology because they have direct applications in the study of animal behavior. There is a beautiful example that illustrates this point. When a snake chases a prey, and the prey hides behind a tree, the snake *stops* chasing. When a wolf chases a prey and the prey hides behind a tree, the wolf *goes on* chasing. The snake is only using *codified rules*, whereas the wolf is adding *interpretation* to them. The wolf makes a "mental jump beyond the appearances," and that is what interpretation is: a "jumping to conclusions," an "abduction" in the true Peircean sense.

And there is more. The behavior of the brain has been studied in the laboratory with mechanisms that simulate its behavior, and *artificial neural networks* are probably the most powerful of such tools. Their ability to create feedback loops allows them to produce a goal-directed behavior, but they also have other outstanding properties. Neural networks have the ability to form *memories*, and a set of memories is the basis of *learning* because it allows a system to decide how to behave in any given situation by comparing the memories of what happened in previous situations (Hopfield 1982; Rumelhart and McClelland 1986; Holland 1992). A set of memories, in other words, amounts to a model of the world that is continuously updated and allows a system to *navigate* in its surrounding environment.

In real life, a system necessarily has a limited number of memories, whereas the world offers a potentially unlimited number of possibilities. Clearly, a real system can never be perfect, but it has been shown that some neural networks can in part overcome this limitation by interpolating between discrete memories (Kohonen 1984). In a way, they are able to *jump to conclusions*, to perform an *abduction* from a limited set of data, and in most cases these guesses are good enough for practical purposes.

This *extrapolation from limited data*, on the other hand, is observed in artificial networks only above a certain level of complexity, and we can therefore divide not only animals but also neural networks in two distinct categories—those that can and those that cannot perform acts of interpretation.

An act of interpretation, like an act of coding, is a process that gives meaning to something, and this is, by definition, an act of *semiosis*. Interpretation, however, is a form of semiosis that is different from coding, because it is based on abduction, and its origin was therefore a real novelty in the history of life.

The origin of animals was a macroevolution that brought into existence a cognitive system based on instincts and feelings (the *instinctive brain*), and later on another major transition allowed some animals to evolve a second cognitive system that gave them the ability to *interpret* the world (the *interpretive brain*).

We realize in this way that the Peircean concepts of *interpretation* and *abduction* have a real explicative power not only in semiotics but in biology as well, and are therefore fully scientific concepts.

Interpretation at the Cellular Level

Free-living single cells (bacteria and protozoa) make up the great majority of the living world, and countless studies have shown that they have a *context-dependent* behavior in the sense that they can react in different ways to different environmental conditions. Thomas Sebeok argued that context-dependent behavior comes from an "interpretation" of the environment, and concluded from this that all living systems, from bacteria to animals, have the ability to interpret the world.

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

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

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

The evidence, in short, tells us that coding and decoding is all that goes on at the cellular level, and yet many biosemioticians have claimed that interpretation does exist at that level *because we can define decoding as a form of interpretation*. There are many examples of this trick in the literature, and these are two of them.

(1) In the paper "What Does It Take to Produce Interpretation?" Brier and Joslyn (2012, p. 154) proposed solving the problem in this way: "…we can identify interpretation in general as any process which encounters a sign and takes it for its meaning in virtue of some code…. Thus a ribosome is an interpreter. And the right amino acid is its interpretation of some codon."

(2) In the paper "Anticipatory Functions, Digital-Analog forms and Biosemiotics," Arnellos et al. (2012) claimed that signal transduction is a process of interpretation because "…receptors act as interpreting systems."

This is what Peircean biosemiotics is about: it claims that interpretation takes place at the cellular level because we can *define* interpretation in such a way that it is present at the cellular level. And this is what caused the break between Peircean biosemiotics and Code Biology.

The existence of meaning in living systems is too important to be reduced to a matter of definitions. It is an outstanding scientific problem, and we can only learn from nature, not from ad hoc definitions, what the semiotic properties of the living systems actually are.

A Critique of Code Biology

Federico Vega has recently published an article entitled "A Critique of Barbieri's Code Biology Through Rosen's Relational Biology: Reconciling Barbieri's Biosemiotics with Peircean Biosemiotics" (Vega 2018). The purpose of the article—explicitly declared in its title—is to show that Rosen's relational biology makes it possible to reconcile Code Biology with Peircean biosemiotics.

As we have seen, Code Biology split away from Peircean biosemiotics because it rejected the idea that processes of interpretation take place at the cellular level, but it is important to underline that this is *not* a rejection of the Peircean concepts. On the contrary, Code Biology fully acknowledges that interpretation is a very real biological process because (1) it takes place in the brain of many animals, (2) it is distinct from coding, and (c) it is uniquely characterized as a process of *abduction*.

What Code Biology rejects, in other words, is not the Peircean concept of interpretation, but the extension of that concept to the cellular level, and this for two reasons: (1) all semiotic processes that we find at the cellular level are fully accounted for by organic codes, and (2) the organic codes are the most conserved entities in evolution, whereas the interpretation processes change according to circumstances.

This means that a reconciliation of Code Biology with Peircean biosemiotics is possible only if it is shown that a genuine process of interpretation takes place inside the cell. This is all that is needed for the alleged reconciliation, but Vega does not limit himself to this point.

Before going into that issue he deals with two other points, and in the Introduction of his article he expresses them in no uncertain terms: "This article shows that Barbieri's rejection of Peircean biosemiotics is based on (1) a limited conception of science, and (2) an incorrect understanding of Peircean biosemiotics" (Vega 2018, p. 2). Vega's critique of Code Biology, in other words, consists of three distinct theses, and the following sections will examine them one by one.

Critique 1: "A Limited Conception of Science"

Vega affirms that, "Barbieri's rejection of Peircean biosemiotics is based on a limited conception of science," but this statement could have two different meanings. It could mean either that (1) Barbieri's mechanistic conception is limited in respect to other mechanistic conceptions, or that (2) Barbieri's mechanistic conception is limited in respect to nonmechanistic conceptions. Vega examines both these cases.

(1) In the first case, Vega compares Barbieri's mechanism with other mechanistic views expressed by representatives of the *new mechanistic philosophy* such as William Bechtel, Carl Craven, Lindley Darden, Stuart Glennan, and Peter Machamer. The result is that the definitions given by Machamer, Darden, and Craver (2000), Bechtel (2007), and Nicholson (2012) are fully compatible with Barbieri's (2011) definition that "mechanism is scientific modeling." Vega reports, for example, that "… Barbieri's explanation of signal transduction codes is comparable to that given by Nicholson of the causal mechanism for the membrane trafficking induced by pain stimulation" (Vega 2018, p. 12). This amounts to saying that Barbieri's mechanism is at the level of most other mechanistic views, so it is not a limited conception in respect to them.

(2) In the second case, Vega compares Barbieri with Rosen and concludes that Barbieri has "a limited conception of science," because he accepts mechanism whereas Rosen has argued that mechanism is not general enough, because it is restricted to computable models whereas biology requires both computable and non-computable models. This is therefore the basis of Vega's first thesis: Barbieri's conception of science is limited because it does not contemplate the existence of non-computable processes.

In reality, Barbieri has published his views on mechanism in the editorial "A Mechanistic Model of Meaning" (Barbieri 2011), and nowhere in that paper is it stated that mechanism is restricted to computable models. More than that, in a subsequent paper Barbieri has argued that *organic information* and *organic meaning* are a new type of observables, called *nominable entities*, whose main characteristic is precisely the fact that they are "*non-computable observables*" (Barbieri 2016, p. 8).

Rosen's idea that mechanism is restricted to computable models, in other words, is an unnecessary limitation of mechanism, just as is Rosen's idea that mechanism is restricted to Newtonian determinism and to reductionism. The important point, at any rate, is that Code Biology does contemplate the existence of non-computable models, and in this respect it is not less general than Rosen's relational biology.

Critique 2: "An Incorrect Understanding of Peircean Biosemiotics"

The second thesis of Vega's critique is that "Barbieri's rejection of Peircean biosemiotics is based on an incorrect understanding of Peircean biosemiotics." This statement is rather vague, if taken by itself, but in the article is expressed in more specific detail on at least three occasions, so let us examine them.

(1) Vega writes that "Barbieri does not adequately distinguish among Peirce's semiotics, Peircean biosemiotics, and interpretation … and within Peircean biosemiotics there are important differences between schools and authors" (Vega 2018, pp. 1 and 15). In reality, all those items are distinguished and discussed in *Code Biology* (Barbieri 2015). More precisely, in that book Barbieri dedicates Section 9.2 to *Physical biosemiotics* (Howard Pattee), Section 9.3 to *Darwinian biosemiotics* (Terrence Deacon), Section 9.4 to *Peirce's semiotics*, Section 9.5 to *Zoosemiotics* (Thomas Sebeok), Section 9.6 to *Peircean biosemiotics* (Thomas Sebeok, Jesper Hoffmeyer, and Kalevi Kull), Section 9.7 to *Hermeneutic biosemiotics* (Anton Markoš), Section 9.10 to *Organic semiosis*, and Section 9.11 to *Interpretation in animal semiosis*.

(2) Vega declares that "Barbieri's definition of interpretation-based semiosis is taken from Posner and not directly from Peirce" (Vega 2018, p. 15). In reality, both sources are used: in Section 9.4 of *Code Biology* Barbieri (2015) reports the definition of semiosis given by Peirce, whereas in Section 9.6 he reports the definition given by Posner, Robering, and Sebeok. More precisely, the definition of Peirce is reported at p. 156 and it is this: "By 'semiosis' I mean an action, or influence, which involves a cooperation of three subjects, such as a Sign, its Object, and its Interpretant, this triadic influence not being in any way resolvable into actions between pairs" (Peirce 1906). The definition of Posner, Robering, and Sebeok is reported at p. 158 and it is this: "The necessary and sufficient condition for something to be a semiosis is that A interprets B as representing C, where A is the interpretant, B is an object and C is the meaning that A assigns to B" (Posner et al. 1997, p. 4).

(3) Vega underlines that the most distinctive feature of Peirce semiosis is the *interpretant* and points out that "… putting the weight on the interpretant rather than on the interpretation would bring Code Biology closer to Peircean biosemiotics" (Vega 2018, p. 15). The role of the interpretant and the comparison of Peircean semiosis with organic semiosis were described by Barbieri in these terms:

> According to Peirce, the elementary act of semiosis is a triadic relationship between A, B and C where A is the interpretant, B is a sign and C is the meaning that A assigns to B.In organic semiosis, the elementary act of coding is a triadic relationship between A, B and C, where A is the adaptor,

> B is an organic sign, and C is the organic meaning that A assigns to B. (Barbieri 2006, pp. 244–245)

These definitions show that the role of the *interpretant* in Percean semiosis corresponds to the role of the *adaptor* in organic semiosis, and putting more weight on the interpretant would be equivalent to putting more weight on the adaptor but would not change the distance between Code Biology and Peircean biosemiotics.

Critique 3: Interpretation at the Cellular Level

Living organisms have been described as *autopoietic systems*, literally "systems that fabricate themselves," because they have the ability to continuously manufacture their own components and to keep them organized into working wholes. This idea has been illustrated in three different ways: first with the theory of "self-reproducing automata" by John von Neumann (1966), then with the theory of "autopoiesis" by Maturana and Varela (1980), and finally with the theory of "metabolism-repair systems," or (M,R)-systems, by Robert Rosen (1991). It must be underlined, however, that these theories have employed different *terminologies*, and this has been, and continues to be, a source of debate and misunderstandings.

According to Rosen, organisms persist in time because they take *antecedent action*, i.e., they continuously fabricate themselves *in anticipation* of a future nonfunctional and deleterious internal state. This amounts to saying that a living system is an "anticipatory system," which is defined as "… a system that contains a predictive model of itself and/or of its environment, which allows it to change state at an instant in accord with the model's predictions pertaining to a later instant." (Rosen 2012, p. 313).

This is the *wording* that allows Vega to conclude that interpretation exists at the cellular level. If the cell is a system that contains a model of itself and/or its environment, "… it seems appropriate to state that *the system interprets* what its model indicates about what might occur in the future from its state in the present" (Vega 2018, p. 16; emphasis in original). This is equivalent to saying that the cell contains an internal model which has traditionally been referred to as *mind*, and it would be legitimate to conclude that every cell is endowed with an *interpretive mind*.

The problem here is that we are given a sweeping generalization about the cell that is entirely dependent upon the *wording* that is chosen to define a self-fabricating system. In the von Neumann theory of self-reproducing automata, or in the classical theory of autopoiesis, there is no mention of internal models that work *in anticipation* of future events, so it is not true that anticipation is a defining feature of self-reproduction. According to these theories, a cell reproduces itself simply by implementing a prefixed set of rules and not because it anticipates what would happen if it didn't.

In the case of the (M,R)-system, it must be underlined that Rosen has never applied it to practical cases, but the evidence tells us that his model is valid for the brain, which indeed has the characteristics of an anticipatory system. In order to prove that those characteristics also exist in the cell, we should be able to find some correspondence between the diagrams of Rosen's model and the biochemical processes of the cell. This study of the biochemical basis of Rosen's model has been the goal of a long-term research program carried out by Jan-Hendrik Hofmeyr, and a first important set of results has already been obtained (Hofmeyr 2007, 2017, 2018).

Hofmeyr has studied the biochemical processes that allow the cell to continuously fabricate its own components while maintaining its overall organization and has divided them into three classes: (1) the enzyme catalysts of covalent metabolic chemistry, (2) the intracellular milieu that drives the supramolecular processes of self-assembly of polypeptides and nucleic acids into functional catalysts and transporters, and (3) the membrane transporters that maintain the intracellular milieu, in particular its electrolyte composition (Hofmeyr 2017, 2018). What comes out is that all the networks and metabolic loops of the cell are fully accounted for by biochemical reactions and by *coding rules*. Nothing else is necessary.

Hofmeyr has achieved in this way a formal integration of Rosen's relational biology and Code Biology, and has also demonstrated the power and the beauty of Rosen's model. The great merit of this model is that it describes the network of relations (hence the name *relational biology*), as a *hierarchical cycle*, and this allows us to see some order in the apparent chaos of cell metabolism. Rosen's model, in short, is a powerful logical tool and when it is applied to the cell it is fully compatible with Code Biology.

Conclusions

Code Biology is a new field of *scientific* research that has two distinct goals: on the experimental side its purpose is to study all codes that exist in living systems; on the theoretical side its purpose is the introduction of *meaning* in biology, an enterprise that is fully comparable to the introduction of *information*, and is equally exposed to all sorts of criticism from all sorts of quarters.

Federico Vega has developed a "Critique of Code Biology" in three theses that deal respectively with the nature of science, the contribution of Peirce, and the existence of interpretation at the cellular level.

(1) On the nature of science, Vega has argued that Code Biology is based on "a limited conception of science" because it is restricted to computable models, whereas Rosen has argued that biology requires both computable and non-computable models. In reality Code Biology does contemplate the existence of non-computable models because it has explicitly proposed that *organic information* and *organic meaning* are "non-computable observables" (Barbieri 2016).

(2) On the contribution of Peirce, Code Biology has fully acknowledged that interpretation is a biological reality in the brains of most animals, and has shown that it is distinct from coding because it is based on the Peircean concept of *abduction*. The two basic concepts of Peirce—interpretation and abduction—have been fully accepted by Code Biology *at the brain level*, but according to Vega this is not enough, and if we stop there we have "an incorrect understanding of Peircean Biosemiotics." One wonders what else should be accepted, perhaps even the idea that there is "an extended mind" in the universe?

(3) On the issue of interpretation at the cellular level, Vega suggests that the operations described by Rosen in the (M,R)-system can be regarded as processes of interpretation. In reality this conclusion relies on the existence in a system of internal models on the world, and the evidence tells us that such models do exist in the brain but not in the cell. This is confirmed by the fact that the other theories of self-fabrication proposed by von Neumann and by Maturana and Varela do not contemplate the existence in the cell of internal representations of the world.

The "Critique" proposed by Vega, in conclusion, is an invitation to reconsider three major points of Code Biology, and criticism should never be ignored, because it can have beneficial effects. In this case, after reviewing the areas critiqued, our conclusion is that those points are much stronger than expected, and Code Biology remains the sole theoretical framework that allows us to introduce the concept of meaning in biology with the traditional methods of science.

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