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Information, programme, signal: dead metaphors that negate the agency of organisms

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SUMMARY

The metaphorical adoption of the concepts of information, program and signal introduced into biology the logic and implicit causal structure of the mathematical theories of information; this is inimical to biology. In turn, those metaphors have hindered the development of a theory of organisms by transferring the agency of organisms to natural selection and to DNA. Moreover, those metaphors introduced into biology the dualism software-hardware and a Laplacian causal structure. Instead, we propose to uphold the agency of the living by adopting three foundational principles for a theory of organisms: namely, 1) the principle of biological inertia (i.e., the default state of cells is proliferation and motility), 2) the principle of variation, and 3) the principle of organization.

Keywords

agency; normativity; theory of organisms; organization; variation; default state; biological inertia; organicism

> "… I have something of a problem with borders: in my peculiar psychic and intellectual economy borders are meant for crossing. More, they constitute irresistible lures." EFK, Refiguring Life: Metaphors of twentieth century biology. Columbia Un. Press, NY1995 ix

INTRODUCTION

Evelyn Fox-Keller's writings on the role of metaphors in constructing biological concepts have enlightened readers regarding the various roles those metaphors played in shaping biological thought. Such writings provided insight into the development of molecular biology, and documented how those metaphors shifted, conflated and shaped a discipline. Metaphors are not neutral devices; they open certain venues for conceptualization while hindering alternative ones. The concepts thus constructed do not demonstrate much precision providing room for change as the field moves along. Her analysis has been useful

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for the understanding of the development of concepts within molecular biology. Our take on metaphors starts from a different perspective. Our aim is to construct objectivity by means of theory; as such, we must watch carefully for the downside of metaphors, exemplified by reification. A brief narrative of our scientific journey may help in understanding our concentration on the perils lurking inside metaphors, rather than on their useful role. This choice has been well analyzed and expounded on by Fox-Keller.

A brief personal detour

Like Fox-Keller, we also trespass into other disciplines. She admitted that these borders are irresistible lures to her. Our trespass was first motivated by necessity. More than three decades ago our experimental results gave us the precious gift of a paradox, namely, that what was taken as fact by the scientific community was challenged by our results (Sonnenschein and Soto 1980, 1999). This unforeseen situation encouraged us to look outside the constraining box of endocrinology, into other areas of biology, and into epistemology. As a result of this process we proposed a biological principle of inertia, the default state, a novelty within this field. Additionally, it made us develop a sort of “physics envy” particularly regarding the abundance of theories in this discipline and its theoretical paucity in biology. We collaborated with philosophers in order to address epistemological issues, and with physicists and mathematicians to delve into theory construction. The objective was to find out how to theorize in biology rather than to force physical and mathematical theories into the discipline as was done previously with the concepts information-program-signal. This query led us to grow as theoretical biologists. Guided by our principles and theories we now venture into experimental biology. Because both the theoretical and experimental perspective imply action in real time, unlike observers such as historians and philosophers, we need to worry about how the metaphors we use could mislead us.

In this journey we observed that mathematicians and physicists seemed to do just fine with their formalisms-while biologists reify metaphors. We thought then that perhaps it would be possible to eliminate these misleading metaphors. Reading Poincaré’s “Science and Hypothesis” we learned that according to him, mathematical reasoning needs and possesses an intuitive content that defies the formal contents. This brought us to the notion that metaphors are unavoidable, so we must resign ourselves to live with them in the sciences and thus redouble our watchfulness.

THE DEATH OF METAPHORS

As originally pointed out by the French philosopher Paul Ricoeur (Ricoeur 1975) all living metaphors involve a structural tension between heterogeneous semantic areas, moving from one attested world of reference to another one that is constructed by this initial tension. The power of a metaphor resides in this tension. Metaphors deal with imagination and fiction; their deployment in science requires vigilance. Indeed, a naked tree is not naked, and a genetic program is not a program. A living metaphor is simultaneously saying “is” and “is not.” When metaphors have been used too often, they die (Ricoeur 1975): we cease to be aware that the metaphoric use of words is not a literal one. This is when they become illegitimate forms of predication and discourse, because they lose the tension between "it is--it is not". Indeed, reified metaphors are dangerously converted into illicit "observables".

THE MOLECULAR BIOLOGY REVOLUTION: THE BIRTH OF INFORMATION METAPHORS

For the last 60–70 years, the notion of information has guided the discourse in biology in general and specially in genetics and molecular biology. Most biologists have embraced this notion, as well as the ones related to program and signal, to the point of adopting them as if they were classical terms in biological discourse. Instead, they are the result of a metaphorical adoption of novel mathematical theories introduced in this realm starting in the 1930's, when Kurt Gödel coded all sentences of formalized mathematics as numbers. Later on, Alan Turing developed this idea further, inventing the Logical Computing Machine for manipulating all sentences of formal theories (Turing 1936); this was done by providing instructions (programs). This is how he invented the mathematical theory of elaboration of information. Both the program and the data were encoded using a sequence of 0s and 1s. This idea inspired Erwin Schrödinger to suggest that information was the discrete observable that should reside in the chromosomes, the "aperiodic crystals" in his parlance. A few years later, DNA's base pair complementarity contributed to reinforcing the use of information metaphors and provided the conceptual frame for the analysis of Mendelian inheritance as well as for the correspondence between DNA and proteins. This is, in brief, how a purely linguistic and abstract context, i.e., information, was transmuted by molecular biologists into the encoding of the Aristotelian 'essence' of an organism into an aperiodic crystal. This metaphorical move unintentionally introduced a causal relationship into biology, which Crick explicitly adopted and proposed as a principle of genetic determination, namely, the central dogma that states that the transcription of the information contained in DNA molecules moves unidirectionally from DNA to RNAs to proteins. Unfortunately, when referring to organisms it has been used to mean from genes to phenotype (Mayr 1961).

The metaphoric use of information also has been influenced by another mathematical theory, Shannon's theory of information, which addresses the transmission of information. In this theory, entropy and information are contravariants; order and information are positively related. In contrast, Turing's and Kolmogorof's theoretical work addresses the elaboration of information. In these theories, information and complexity are positively correlated with disorder and entropy and are contravariant with order. Hence, for the most part, when biologists speak of information, they do not specify which, if any, is the proper relation of biological information with entropy. In brief, information, program and signal in biology are not proper theoretical entities, but just metaphors linking the current use of these terms with the theoretical ones enunciated in rigorous mathematical theories. Moreover, these mathematical theories are purely abstract, and do not pertain to physical or biological entities (Longo et al. 2012). Due to this and other lacks of congruency between the theoretical use of these terms in mathematics and their metaphorical use in biology, some biologists and philosophers have raised objections "on the ground that enthusiasm for information in biology has been a serious theoretical wrong turn", and because "it fosters naive genetic determinism" (Hacking 1999, Godfrey-Smith and Sterelny 2011).

Our analysis of the “migration” of information theory into biology has addressed the differences between these theories regarding the relationship among complexity, information and entropy. We concluded that the logic and implicit causal structure of the mathematical theories of elaboration and transmission of information make them deleterious to biology (Longo et al. 2012). The problem is not solved by claiming that biologists use ‘information’ in a metaphoric way. By their implicit content, the information metaphors may stealthily impose a way of thinking that, by hiding their bases does not allow for a critical insight. In this regard, the hidden allusion to mathematical information brings about the idea of discrete data types and of coding. Anything else is considered “noise”, which could only increase disorder. Mechanical forces acting on a computer or a wire will only decrease the information that they are elaborating or transmitting. The physical world poses a problem for those that see DNA as information, because DNA is mechanically and geometrically constrained by the chromatin fiber structure that contains it: if DNA is digital information, the torsion forces resulting from the structure of the chromatin fiber could only decrease information, as happens when “noise” is introduced by the physical deformation of a transmission cable (Lesne and Victor 2006).

Contrary to the hard Laplacian determination implied by mathematical coding, as Hull discussed, geneticists in the 1910s and 20s already knew that the relationship between genes and phenotypes is not univocal (Hull 1974). He called it the problem of “the many (genes) and the many (phenotypes).” Neither is the gene-protein relationship. This lack of univocal correspondence between a given gene and its proteins is demonstrated by alternative splicing and by the fact that protein folding is not entirely determined from its amino acid sequence (Kang and Kini 2009). Additionally, the recent discovery that a large fraction of the proteome is intrinsically disordered, and that these proteins are functional contradicts the notion that protein folding is entirely determined from its amino acid sequence as expected from the central dogma (Toto et al. 2020). Moreover, the stochasticity of gene expression is an objective demonstration that genes do not have a privileged causal role (Kupiec 1983). As an example, protein and mRNA copy numbers vary from cell to cell in isogenic bacterial populations; also, in a given single cell, protein and mRNA copy numbers for any particular gene are uncorrelated (Taniguchi et al. 2010). Those adhering to the information paradigm interpret these fluctuations as “noise”, implying that the perfect Laplacian determinacy of the digital information paradigm meets the “imperfect” physical reality of the cell. Up to here and as long as one is interested to go for DNA to RNA to protein, rather than to phenotype, the challenging problems briefly mentioned above may be somehow circumvented by the addition of inelegant/clumsy *ad-hocs*. But as soon as we move from biochemistry to dealing with organisms, be they unicellular or multicellular, the conceptual problems become crippling (Longo et al. 2012).

ORGANISMS LIVE IN A MATERIAL WORD, NOT IN A MATHEMATICAL ONE OF 0’S AND 1’S.

The ontogenesis of a sexually reproducing metazoan starts at fertilization. The resulting zygote is both a cell and an organism. This dual identity means that organization levels are entangled from the very beginning of development; this makes the study of causality difficult. During embryogenesis, mechanical forces are main causal contributors to organogenesis through their continuous production of deformations; from gastrulation (Farge 2003, Merle and Farge 2018), to organogenesis (Shyer et al. 2013). In contrast, the metaphorical use of information encourages the observer to think in terms of discrete structures, that is, of molecules. In this view, molecules are the place where information is contained in the form of a digital code, as stated in the central dogma, from DNA to protein. How could this idea apply to the constraints imposed by interactions among cells, structures and organs in living organisms or by the ecosystem where these organisms reside? New *ad-hoc* concepts are created such as to "transduce the signal" from a physical force or a molecule that is not a protein, to a protein, usually a receptor, which supposedly is digitally encoded as a molecular sign. This is just one of the deleterious contributions of "information" to biology, namely, that causes have to be found in molecules, in DNA, whenever possible. Thus, the strong evidence for a decisive role of biomechanics during both morphogenesis and tissue remodeling argues against the existence of a developmental program or information in the sense of a "code-script" within the genome (Longo et al. 2012). The adoption of the concepts associated with information, like program and signal, makes the organism fade to the point of becoming a result of the agentive properties of genes. François Jacob, Ernst Mayr and others welcomed the idea of program because by simply swapping teleology for program they could avoid a long-standing debate about the nature of the living matter. Teleology, that is, explaining something as a function of its goals, was offensive to scientists embracing mechanicist stances (Peluffo 2015, Mayr 1961). In Jacob's own words: "For a long time the biologist has been consorting with teleology as with a woman without whom he can't live, but with whom he doesn't want to be seen in public. To this hidden relationship, the concept of program gives a legal status" (Jacob 1973). In sum, the program and information metaphors hindered the study of embryology because they ignored the important role of the environment in the determination of phenotypes and in developmental plasticity. The transfer of agentive properties to molecules other than genes, such as hormones, has also created an image of cells and organisms as passive consequences of internal (genes, hormones, etc.) and external agents (natural selection) (Soto and Sonnenschein 2018).

THE RADICAL MATERIALITY OF LIFE

In previous publications, we concluded that the strong form of dualism ingrained in physics and in the computational world (software-hardware) seems unsuitable for biology. After all, life is based on the distinct materials organisms are made from, namely, particular DNA, RNAs, proteins and membranes. Unlike hammers that can be made of diverse suitable materials, there is no way to dissociate the specific materials that make a living organism from the functions this organism accomplishes (Longo and Soto 2016). Giuseppe Longo felicitously calls this "the radical materiality of life" which rules out the software-hardware dualism in biology.

Differences between the inert and the alive require the adoption of different scientific approaches to study them. In this regard, we have argued that it is pointless to try to fit biology into physics on the basis that a prebiotic world preceded the advent of life. Life is not a particular case of the physical "world"; probably it is the opposite. In spite of this common belief among biologists, we cannot, in fact directly address the "real world". We do it indirectly by means of the scientific disciplines constructed by the human mind to understand such a world. Hence, we seek to find coherence between the two disciplines. The physical components of organisms and organisms as physical objects do "obey" the laws of physics. However, additional principles may be necessary to understand organisms as living beings. Organicism provides a world view from which to seek those principles.

AN ORGANICIST PERSPECTIVE

To right the wrongs: the return of agency

In the 20th century, agency, a property of organisms that traditionally served as a quality to distinguish the alive from the inert, has been transferred from the organism to various entities, including natural selection (Moss 2003, Walsh 2015) and genes and proteins (Fox Keller 2015). Organisms are agents whose main aim is to keep themselves alive; their proper understanding requires teleological principles of explanation. After the failure of the mechanicist view in its latest incarnation, namely, the organism as a computer, organicists are now in the process of bringing agency back where it belongs, the organism.

Organicism has its philosophical bases in Aristotle and Kant and in their conception of the organism; the vital force invoked by Kant's followers was comparable to universal gravitation: i.e., mysterious but not necessarily contradicting the physical principles of the 18th century. In the 20th century it reappeared in a materialist frame conceptually related to self-organization. According to Gilbert and Sarkar, organicism is a materialistic philosophical stance that, contrary to reductionism, considers both bottom-up and top-down causation (Gilbert and Sarkar 2000). Others explained emergence without downward causation (Mossio, Bich, and Moreno 2013). In both interpretations, new properties that could not have been predicted from the analysis of the lower levels appear at each level of biological organization (Soto and Sonnenschein 2006). Also, implicit in this view is the idea that organisms are not just "things" but objects under relentless change. Given the importance of change both in ontogenesis and evolution, some philosophers have considered them as processes rather than things (Whitehead 1929, Koutroufinis 2014, Dupre and Nicholson 2018).

OUR VIEW ON ORGANICISM

Central to our organicist perspective are the following concepts 1) organization, 2) historicity 3) organisms as agents, and 4) specificity.

Organization:

Organization is an exclusive attribute of life and of machines invented by humans. Closely related to the concept of organization is the notion of "organizational closure", which is a "distinct level of causation, operating in addition to physical laws, generated by the action of material structures acting as constraints" (Mossio and Moreno 2010).

Historicity:

Far-from-equilibrium physical systems like flames and micelles are ahistorical because they appear spontaneously. In contrast, organisms are a consequence of the reproductive activity of a pre-existing organism. Thus, understanding biological organization requires a historical analysis (Longo and Soto 2016).

Agency:

Organisms are agents; namely, they have the capacity to generate action and their own rules[1]. Organisms change their environment and they change themselves during ontogenesis. Agency is a major distinction between the living and the inert. Organisms undergo individuation which is manifested by their ability to change their own organization. Another remarkable characteristic of organisms is their propensity to become sick, and to return to health. In this regard, Bichat stated: “there is no distinction between normal and pathological in physics and mechanics”(Canguilhem 1991). Associated to the notion of autonomy and agency is the notion of teleology. The goal-directedness of organisms is viewed as a causal consequence of the architecture of adaptive systems (Walsh 2015).

Specificity.

The objects of physics are generic and thus interchangeable, like rocks and planets. Instead, biological objects are specific, i.e., they are individuals permanently undergoing individuation. Hence, variation in physics is a result of measurement error; while in biology, as Darwin already realized, in addition to this source, variation is intrinsic to the properties of organisms (Longo and Montévil 2011, Longo and Soto 2016).

Biological Causality

In classical mechanics, it is relatively simple to identify a theoretical cause. According to the principle of inertia, if no force modifies the state and properties of an object, the object conserves its state and properties. A theoretical cause would then be a force that modifies the state and properties of the object in question. Organisms instead are generated by other organisms; thus, there are many “causes” in action forming a complex chain from the first ancestor to say, modern humans. Additionally, biological entities are able to generate action and are normative. These properties imply that the organism has choices and, among them, may pick the “wrong” ones. This inherent ability of biological entities poses challenges to the classical notion of theoretical cause.

A requisite for identifying theoretical causes is to have a theory. Biology does not have a global theory of organisms to provide access to theoretical causes. We suggest instead to use the term “constraint” which is used in Evolutionary Biology to indicate factors that limit the production of phenotypic variants. In our view, a constraint is a factor that will change the range of possible outcomes. A negative constraint will narrow down the range; a positive one, instead, will increase the range of the possible. A constraint may also hinder certain outcomes while enabling others: “For example, during rodent perinatal development,

[1]The actions of these organisms are not mere effects, but are performed according to a goal-these actions have a normative and teleological dimension (Moreno 2018, Soto and Sonnenschein 2018)

estrogens masculinize the hypothalamus, thus narrowing the feedback repertoire to just the negative one, while in the absence of estrogens the hypothalamus expresses both positive and negative feedback" (Soto, Longo, Montévil, et al. 2016).

Differences between the inert and the alive require the adoption of different scientific approaches to study them (Longo and Soto 2016). In this regard, we have argued above that it is pointless to try to fit biology into physics on the basis that a prebiotic world preceded the advent of life. Life is not a particular case of the physical "world". We scientists do not, in fact, directly address the "real world". We do it indirectly by means of the scientific disciplines constructed by the human mind to understand such a world. Thus, we seek to find coherence between the two disciplines. The physical components of organisms and organisms as physical objects do "obey" the laws of physics. However, additional principles may be necessary to understand organisms as living beings. Organicism provides a world view from which to seek those principles.

From philosophical stances to theories

Theories are central to scientific practice. Scientific theories provide organizing principles and construct objectivity by framing models, observations and experiments. Biology has only one global theory that addresses the long-time scale of phylogenesis, which for the last 150 years has provided an appropriate framework to study evolution. Since its inception, the theory of evolution has been modified and continues changing as conceptual problems are identified and new observations arise prompting the need for reconciliation of theory and data (Huang 2012, Noble et al. 2014, Walsh 2015). In contrast, biology has yet to produce a comparably efficacious theory of organisms that will encompass the whole lifecycle.

In our analysis, reductionist approaches including the introduction of notions borrowed from mathematical theories of information have at best increased our knowledge of aspects of biology that today pertain to the disciplines of biochemistry and molecular biology. In the meantime, it has hindered the development of a proper theoretical frame to study organismal biology. Meanwhile, organicism and its predecessor, vitalism, have provided an adequate frame for the success of embryology and physiology. A first step towards the elaboration of such a theory of organisms is the identification of foundational principles. These principles have to address the salient properties of organisms such as agency and normativity and the ability of organisms to harmonize their ability to generate novelty while maintaining stability and remaining at the same time plastic and robust (Soto, Longo, Miquel, et al. 2016).

PRINCIPLES FOR A THEORY OF ORGANISMS

We have identified three principles for a theory of organisms (Soto, Longo, Miquel, et al. 2016). Starting from the cell theory, and acknowledging the agency and normativity of biological objects, we have proposed a ***principle of biological inertia***, or "default state" of proliferation with variation and motility (Soto, Longo, Montévil, et al. 2016). This principle is the biological equivalent of the principle of inertia in classical mechanics. It states that given an appropriate supply of nutrients and physiologically adequate conditions (temperature, pH) all cells, be they prokaryotes or eukaryotes, belonging to unicellular or multicellular organisms, will proliferate constitutively generating variation and exerting their ability to initiate movement. This principle is closely related to the radical materiality (in contraposition of the substrate independence of information) and to the agency of living objects. In addition to the default state, we have adopted the ***principle of variation***, which is manifested at all levels of biological organization. Each iteration of a morphogenetic process is a source of variation and thus a potential source of novelty and plasticity (Montévil, Mossio, et al. 2016). Finally, the ***principle of organization*** is the fundamental source of biological stability. The notion of closure of constraints is the means to achieve and maintain stability (Mossio et al. 2016). In addition to this theoretical purpose (Soto, Longo, Miquel, et al. 2016), these founding principles have been useful for framing experiments. (Sonnenschein and Soto 2016) and mathematical modeling (Montévil, Speroni, et al. 2016) and for providing a better understanding of endocrine regulation of metabolism (Bich 2020).

CONCLUSION

The uncritical adoption of reductionistic frameworks and metaphors inspired by mathematical theories of information are a main cause of the problems that are plaguing current biological practice. The aim of briefly describing the principles for a theory of organisms here is to illustrate that organicism provides sound guidance to the quest for veritable biological principles, thus opening the possibility of constructing the theoretical frame needed to produce an autonomous and mature biological and biomedical science.

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