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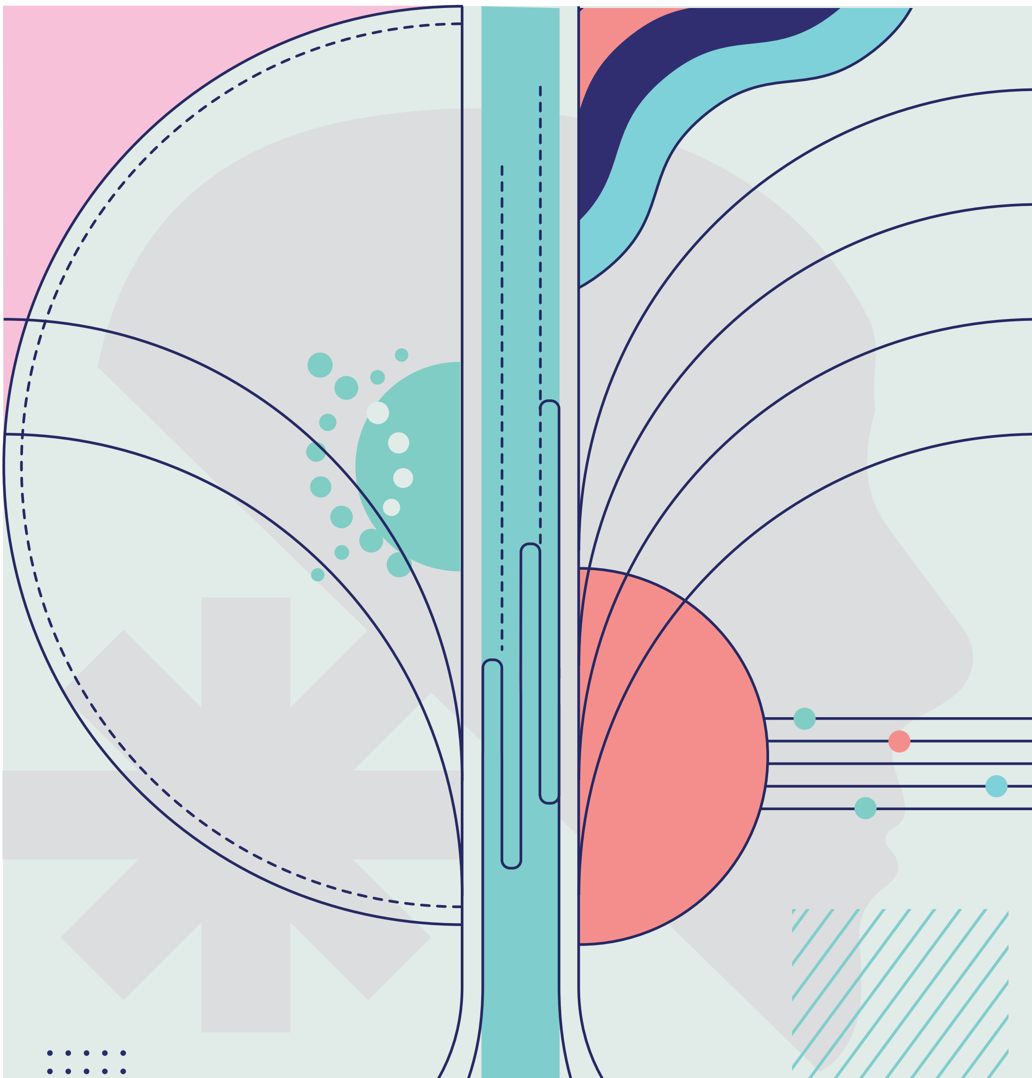

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Editorial

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Epigenetics and/as complexity

2.1 Introduction

The history of spearhead science is one of strong advancement and, indeed, severe or radical revolutions. If according to a reliable source, just one of the most prestigious journals in the world –*Nature*– publishes around 20000 articles a year (Cfr. Journal *Scientometrics*), and, furthermore, in no other age had mankind known the existence and joint work of so many researchers, engineers, PhDs, and scholars, then a bright light is shed onto the intellectual and technological panorama of our days. We all, it appears, are the outcome of such progress and rhythms, and at the same time direct or indirect agents of the ongoing scientific and technological revolutions.

To be sure, one of the branches of such advancement is epigenetics, a most recent intellectual achievement. Epigenetics can be traced back originally to the works by Belyaev and his group, Waddington and Schmalhausen, Lindquist's group, Ruden and his group, and more recently, to the research on prions. This is a story that goes from the 1940s until very recently, and from the USA to England and the then existing USSR. However, it is around the 2000s when epigenetics is properly born.

Epigenetics allows overcoming the strongest of all dualisms, namely, between nature and culture. This is undoubtedly its most salient landmark. Nonetheless, its mechanisms are elementary: methylation, modification of the proteins of histones, and non-coding RNA. After these three factors, biology becomes culture, and culture is embodied as biology. This text claims that epigenetics is one of the sciences of complexity and brings out arguments and justifications.

Such is, indeed, our endeavor here. We claim that epigenetics leads to complexity, *i. e.*, the sciences of complexity, and, *à la limite*, it can be said to be one of the sciences of complexity. In order to support this claim four arguments are provided. First, a brief presentation of epigenetics is brought out in which several features that pertain to complexity science are outlined. The second argument is that complexity science is concerned with systems, behaviors and phenomena that generally speaking point out toward overcoming dualism. The gate, so to speak, is wide open for an encounter between epigenetics and complexity science. On this basis, the third argument digs into what epigenetics is, how it works and what it entails. The fourth argument sustains that it is life and the understanding of life what serves as the ground for bringing together epigenetics and complexity science. At the end some conclusions are drawn. Summing up, epigenetics is about bringing together nature and culture (nature and nurture), genetics and history, genotype and phenotype, development and evolution –a most innovative and challenging endeavor.

2.2 Epigenetics, revisited

Epigenetics can be conceived as heritable changes in gene activity and expression that take place without any alteration in the DNA sequence. In other words, it is perfectly possible that living systems in general and human beings in particular, inherit experiences that alter the genes and yet do not modify the DNA sequence. Briefly said, culture can be inherited and still leave the DNA unchanged. Furthermore, culture can be transmitted without altering the DNA, which, by definition, is unique. It is a most surprising happening when viewed with the eyes of tradition. It is, indeed, a wonderful development and contribution from biology to the wide understanding of science, history, and culture.

Now, changes in the gene expression refer to the phenotype, and changes in the gene expression occur that leave the DNA unchanged. Thus, contrarily to what was normally thought in biology, it is perfectly possible that genes change without necessarily altering the structure of the DNA. The mechanisms of inheritance and variation are much more subtle and complex that previously thought. Over against the traditional understanding in biology, Darwin and Lamarck are united precisely thanks to epigenetics.

Epigenetics has a rather long history behind that encompasses the 1940s until some years ago. It goes from USA to England to the USRR, even though a most important antecedent is to be found in the work by D'A. Thompson (1992) about mathematics and biology, and particularly about the role of morphology in the understanding of life, *i. e.*, living beings. Furthermore, epigenetics can be traced back in the works and research by Belyaev and his group, as well as in the ground seeding out by Waddington and Schmalhausen. Not least, Lindquist's group is also influential in the origins of epigenetics, not to mention, on the other side, more recent contributions by Nanney. Later on, Ruden's research team is to be accounted for the origins of epigenetics, too, up until more recent research around prions brings the final conditions for the emergence of epigenetics. All in all, however, epigenetics can be properly said to be born in the early 2000s, particularly thanks to the work led by E. Jablonka (2006).

Epigenetics could have been born around the midst of the 20th century. However, the emergence of molecular biology impeded epigenetics to being born before. A reductionist research program triumphed over a more integral and complex-theoretical approach to life and living beings. Nonetheless, along the years, since Waddington's pioneering contributions, a rather large field has emerged giving rise thereafter to a variety of interpretations and scopes that sometimes make it difficult to accurately define it.

Since then, a most compelling challenge to a mechanistic, deterministic, and reductionist understanding of life and health has been produced in spite of there not being as yet a clear-cut definition of the concept (Villota-Salazar *et al*., 2016). Instead, a more organic, or complex understanding has emerged that allows superseding a radical or fixed division between, say, genotype and phenotype, or also, between nature and culture. The traditional reductionism of Darwinism, Neo-Darwinism and classical genetics has come to be challenged by epigenetics, allowing a unification of Darwin and Lamarck thanks to the already well-established fact that, under certain circumstances, some acquired traits can be heritable in organisms. As a consequence, epigenetics sets the ground for a much better, say deeper and wider understanding and explanation of what happens in life and health to the living systems, and how we can and must approach them.

The possibility to reject reductionism –in the midst of a discussion about the extent, scope and definition of epigenetics– sets the ground for a more encompassing understanding of the tenets of evolution and biology. Without exaggeration biology is enriched to the point that both the evolutionary and the developmental approaches come to be united bringing out a most refreshing view of life, *i. e*., living organisms.

Epigenetic mechanisms have been observed in plants, animals –particularly mammals, and humans, crossing up, so to speak, a bridge that allows for a more complex understanding of, on the one hand, the relationship between genotype and environment, and on the other hand, between the various levels of stances of living beings. Life has much more in common within the various realms or domains than it was previously thought. Genetics, systems biology, and now developmental and evolutionary biology provide a more ample and yet robust view of life at large. There is not a clear-cut boundary between living organisms and their environment, or between the experiences of the environment (Umwelt) and the way in which those experiences are both inherited and transmitted. Epigenetics opens up the gates, so to speak, for an understanding and explanation of life along the way of complexity science.

2.3 An overview of the sciences of complexity

Generally speaking, the interplay between evolution and development that epigenetics allows can be understood as a sort of *holistic or systemic* view in which all parts are related to each other, and yet the whole is more than the sum of the parts. Thus, the original question about the function of cells and their differentiation set out by Waddington in the framework of the discussion between preformationists and epigenesists. However, more than just a systemic view of development and evolution, epigenetics sets the ground for a complexity theory approach.

Indeed, complexity science is about an understanding of how inflections, ruptures, discontinuities happen –and how it is possible to introduce new *degrees of freedom* into the reality and the world. The rupture that epigenetics introduces has to do with breaking down reductionism and determinism, particularly genetic determinism –such is most notably the case when studying and explaining (epigenetic) cancer– and biological determinism that presumably does not have anything to do with learning, experience and culture at large.

To be sure, complexity science is about increasingly complex systems, non-reductionism, non-determinism, and non-linearity among several other salient characteristics of what a complex system, phenomenon or behavior is. Certainly, these appear to be negative features of a complex system, and yet they point directly to the core of what life and living systems are –over against a physical, chemical, or even biologist reductionism.

Regarding the very explanation of living beings in general, epigenetics shows that the interplay between nature and culture is indeed a dynamic process triggered by mechanisms such as methylation. Culture is inherited and transmitted genetically very much as nature is experienced and incorporated in the midst of our DNA –something that was unimaginable before the pioneering work of Waddington and his successors, and is still unimaginable for normal, conservative, dualist science.

Complexity science is much more than –and still quite different to– a systemic or holistic approach. Rightly understood, the sciences of complexity are about degrees of freedom, namely about how complex systems gain degrees of freedom very much as how the very degrees of freedom define complex behaviors. In this sense, epigenetics matches the same spirit in that the understanding of the interactions between phenotype and genotype. Moreover, openly said, the relations between genotype and phenotype are non-linear, very much as the interactions between the organism (genes) and the environment are non-linear, too.

Non-linearity means that in development and evolution the input and the output are not proportional. The outcome cannot be anticipated by the input, and the input does not determine the outcome. If this makes sense, then the claim can be made that there is a path that leads straightforwardly from epigenetics to the sciences of complexity, or also, that epigenetics is one of the sciences of complexity. Such a claim will be further sustained throughout the following sections.

2.4 Logics and mechanisms of epigenetics

Epigenetics takes place mainly via methylation of the DNA. There are other ways in which epigenetic evolution happens, such as phosphorylation, but methylation has been identified as ruling largely the process. Methylation occurs as a remodeling of chromatin and as a modification of the histones. The epigenetic code is tissue- and cell-specific, whereas the genetic code in each cell is the same. It follows that the epigenetic code is much more ductile in operating, which has important consequences for the understanding of both of them, the individuals, the species, and evolution.

The epigenetic mechanisms are affected by the development of the individual as well as by its own evolution, by environmental chemicals and in general environmental processes –waters, air, music, and vital experiences–, by diet and aging. To be sure, the mechanisms of epigenetics never cease along the life of an individual, and certainly not in the course of the evolution of the species and the environment in which life strives to be possible.

Briefly said, living is about epigenetically changing, incorporating experiences, expanding and transmitting them on to the following generations, even if there is not offspring again or it has never happened.

Paradoxically, epigenetics was born thanks to the studies on the methylation of DNA and the role of chromatine, which gives the impression that there is a sort of reductionism in the mechanisms of epigenetics. Such an impression, however, can be superseded when acknowledging that the epigenetic control of the gene expression was initially reckoned in relation with the problem of differentiation, *i. e.*, how cells (of an embryo) can change into other types of cells.

Thus, as it is well known, cells do split almost unceasingly (renewal of cells and tissues). Yet, there is a limit about the number of times a cell can split. The reason lies in telomeres. Apparently the telomeres in women shorten much more slowly than in men, so much so that longevity in females is more robust than in males –at least for the case of human beings.

Now, when they are too short telomeres impose a limit to the life of a living being, for telomeres cannot be methylated. The crux here is that epigenetics can be viewed as a process of becoming immortal, at least in the sense of inheriting and transmitting experiences genetically. Not only does culture allow for some sort of immortality –say, Mozart, Beethoven, or Mahler, to name but just some cases. It is to be highlighted that methylation on its own is neither good nor bad; it all depends on the segments of the dna that are methylated.

Being as it may be, the key about epigenetics lies widely in development –where after it affects the way in which development affects evolution– of species. Development arises then as the stance in which evolution happens –a clear Lamarckian appreciation. Individuals seem to emerge as the crucial stance of inheritance and learning –two distinct and yet distinctive landmarks of evolution.

Epigenetic changes happen because of two main reasons, namely the role of stress upon an organism (huge indirect changes in the long run), and the existence of sleepy (inactive) genes or the existence of epigenetic landscapes. It is the conjugation of stress and epigenetic landscapes which provides, generally speaking, the rationale for epigenetics. In any case, histone modifications, DNA methylation and the activity of non-coding RNA (ncRNA) can be clearly identified as the mechanisms of epigenetic regulation. As it is well known, histones are proteins around which DNA can wind for compaction and gene regulation.

This concept is to be highlighted: regulation. Epigenetic mechanisms regulate the way in which experiences, and epigenetic landscapes can be organically incorporated –moreover, embodied. Development and evolution are certainly not parameters or frameworks for the understanding of life and living systems. More exactly, development and evolution are embodied –the embodiment carried out, so to speak, via histone modifications, DNA methylation, and the activity of ncRNA.

Epigenetics at the same time complements and overcomes traditional Darwinian explanations, very much as the classical Lamarckian understandings. Differently said, the epigenome links the genome and the environment.

As it is well known, the epigenome can be seen as the genome-wide distribution of chromatin modifications or DNA methylation that may include non-heritable changes or genetically influenced patterns. Even though there are many histone modifications, the best-studied ones are acetylation, methylation and phosphorylation. The core here is that even though epigenetics has been studied in a central process, namely methylation, it takes place via a further variety of forms –acetylation, and phosphorylation.

2.5 Understanding life as the most complex phenomenon, ever

The ground can be safely set out to understand that there is a strong link between complexity and epigenetics, something that has never been brought to the fore before. I would like to highlight three traits that make such a link possible.

- *Life as well as health is to be grasped as a synthesis.* Synthesis is, indeed, the very form in which life, *i.e.*, living systems takes place, evolve and evolve. Departing already from the nucleosynthesis in the backstage of the universe in the middle of exploding stars down to the synthesis of ions, biopolymers, and metabolites, synthesis pervades life and makes possible life as such. The language of chemistry rather than that of physics is more than suitable here. It is easy to think in this context about the synthesis of proteins, the synthesis of imagination, the synthesis of perception and also, necessarily sex as synthesis. Other forms of synthesis that can be mentioned here are graphs and hyper-graphs, the synthesis of and as maps, and not ultimately modeling and simulation as forms of synthesis.
- *The issue at stake is life, i.e.,* health. As it follows consequently, it is life and health what is truly at stake when understanding synthesis. Epigenetics is a science that enables thinking in terms of synthesis –here the synthesis between nature and culture thanks to the discovery of the quartet chromatin,

methylation, NCRNA and histone modifications. This idea can be translated as follows: sickness and disease can be grasped and treated in analytical terms; perhaps they must be considered analytically in order to defeat them. However, health and life demand a quite different mindset, namely thinking in terms of synthesis. Epigenetics and complexity science open the door widely to such a mindset.

- *Life, i.e., health is a highly increasingly complex system.* Learning and adaptation are the key features of and that serve as rationale of evolution. Learning can be grasped as the sine qua non condition for adaptation; in any case, they are both unceasingly open and changing. It is such unbreakable capacity of learning and adapting that makes life possible according to the changes in the environment –something that in general living beings cannot control. Epigenetics is to be viewed as an increasingly and continuously adapting process of heredity and variation. As such, it comes as an alternative to Darwinism and Neo-darwinism. The ways in which adaptation occurs are highly enriched thanks to epigenetic mechanisms.

Life is not just the outcome of natural processes, say natural selection, or sheer cultural and volitional circumstances. Epigenetics has been studied and proved in plants, animals and human beings, so far. As a consequence, epigenetics can be integrated as one of the sciences of complexity in that it enriches, widens up and enlarges the understandings carried out by sciences and disciplines such as non-linear thermodynamics, chaos theory, catastrophe theory, complex networks, fractals, artificial life, swarm intelligence, self-organized criticality and self-organization, to name but just some.

Thus, a generous panorama for the understanding of life and living beings appears that encompasses symbiogenesis, systems biology, evo-devo, eusociality, and epigenetics –to the already rather well established explanations brought by Darwinism, Neo-Darwinism, Lamarckism, biochemistry, molecular biology, and others.

The phenomenon of life is much richer than previously expected. Analytical approaches and explanations are not only wrong because they are partial, but also hinder dynamic and synthetic views of what happens in life and to life in general. As mentioned, the most wonderful and general of all synthesis is the one between nature and culture. Epigenetics, to be sure, is the science that most contributes to overcoming the splitting between them and regarding them as a solid and yet dynamic unity. The crucial stance where epigenetics takes place is the living cell.

In other words, against the appearance of a genetic reductionism in some explanations of life, and the focus in the individuals of a species, for instance, epigenetics focuses on a stance that was never before considered carefully, namely the living cell. The study of cells, hereafter, stands as the interface between nature and culture. It goes without saying that the minimal consideration here is about eukaryotic cells –without leaving aside that there is a strong discussion about questioning a previously considered sharp boundary between eukaryotic and prokaryotic cells. Reasons for optimism in research appear fresh and sound in the upcoming horizon.

2.6 Conclusions

Three conclusions can be safely brought out from what precedes:

- Epigenetics is an open gate that leads to complexity, *i. e.*, the sciences of complexity.
- *À la limite*, epigenetics can also be said as being one of the sciences of complexity.
- Straightforwardly said, complexity is about overcoming dualism and a binary view of reality and the world.

The interplay, if not complementarity or even integration between the sciences of complexity and epigenetics is a most compelling chapter from the standpoint of history and philosophy of science. Epigenetics has been studied in human beings, animals, and plants –which is indeed a major achievement for any theory or science. A cross-disciplinary, integrative or unified view of nature and the universe, of life and society is a clear sign of intelligence and challenge. Both epigenetics and complexity theory can be said to share a consilience-like view of life.

Furthermore, epigenetics can be safely viewed as one of the sciences of complexity. In this respect:

- Epigenetics can be taken as a complex approach of life and health –at the scale of human beings.
- It remains an open-ended question how it works for animals and plants, even though it has been studied and tested. Future research will provide a more unified view of life, very much as it has already happened

> with genetics, genomics, or systems biology –in the sense that epigenetics be enlarged to more than three generations, which is the current time span in which it has been verified; and, additionally, it can bring clearer lights about other mechanisms. The youth of epigenetics stands in favor of an optimistic view about its future –for research and science.

As it is well known, a single DNA sequence gives rise to more than 400 different cell types only in humans. The question arises as to how to identify the epigenetic marks for each cell type. Major research programs are undergoing aimed at explaining this question, such as the International Human Epigenome Project (AHEAD), the Human Epigenome Project (HEP), and the NIH Roadmap Epigenomics Project –three colossal programs with a strong scientific and financial muscle. The future of epigenetics remains wide and deep with optimistic horizons.

Not least, the fact that the classical hallmarks of human cancer can potentially be achieved "purely" through epigenome deregulation questions the current view of tumorigenesis, suggesting that epigenome deregulation may cause cancer without genetic contribution. In medical terms, cancer is a "complex disease". However, "complex" refers here to the intertwining of genetic, environmental and life-style factors that trigger the disease. Not that cancer is non-linear, for instance. To be sure, cancer, which is one of the most salient research programs relating genetics and epigenetics, brings to the fore the complex interplay between gene (de)regulation, and experiential, social or existential moments in the life of a person.

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