Epigenetics and Anticipatory Processes: From the Empirical to Foundational Aspects

Mihai Nadin

Abstract The making and remaking of the living can be described from a variety of perspectives. The genetic and epigenetic aspects of life dynamics are focused on the reproduction of organisms. Reproduction of life is never a repeat, but rather always an original. The anticipatory nature of life is ontological in nature. There is no life in the absence of anticipatory processes. Understanding interaction is the premise for a coherent foundation for the study of the relation between epigenetics and anticipation.

Keywords Interaction · Creativity · Non-determinism · Multicausality · Meaning

1 Conundrum

Epigenetics goes back to Aristotle:

> For e.g., an animal does not become at the same time an animal and a man or a horse or any other particular animal. For the end is developed last, and the peculiar character of the species is the end of the generation in each individual.

(Although not everyone agrees on the significance of his findings, [1, 2]).

This view distinguishes itself from the doctrine of preformation accepted during Aristotle's time. Instead of agreeing that the "end" features are fully formed in the zygote, the Stagirite argued in favor of gradual development from an undifferentiated origin, i.e., from the genesis. All this was based on empirical observations. He called the process *epigenesis* (Aristotle, *On the Generation of Animals*). In 1942, Conrad Waddington [3] focused on "the processes…by which the genes of the genotype bring about phenotypic effects." In defining the "epigenotype," Waddington echoes Aristotle's idea: "…between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes." His view, not unlike

M. Nadin (✉)
antÉ—Institute for Research in Anticipatory Systems, University of Texas at Dallas, Richardson, TX, USA
e-mail: nadin@utdallas.edu
URL: https://www.nadin.ws

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Aristotles', is based on the empirical. (We are not rehashing the history of the concept, but rather taking note of significant moments.)

Not surprisingly*, anticipation* goes back to Aristotle as well [4]

> .... if every instrument could accomplish its own work, obeying or anticipating the will of others ... if the shuttle weaved and the pick touched the lyre without a hand to guide them, chief workmen would not want servants, nor masters' slaves.

The notion of *prolepsis*, signifying foresight, originated at that time. *Antecapere ergo sum* is the formulation advanced [5] as the counterclaim to Descartes's "Dubito ergo sum"—more precisely, opposing anticipatory action to reaction (as a reductionist-deterministic process). It took almost as long as the time between Aristotle and Waddington's interest in epigenetics until Whitehead [6] suggested that each process involves the past and anticipation of future possibilities. Inspired by Whitehead and Burgers [7] went on to identify choice as coextensive with anticipation. Bennett [8] suggested that anticipation is "the basis for adaptation." After that, psychologists gladly adopted the subject, but missed its meaning. Before all of them, however, there was an impressive Russian/Soviet School—N. A. Bernstein, Alexei Ukhtomsky, Natalia Bekhtereva, Peter Anokhin, Dimitri Uznadze, Ivane Beritashvili, and Alexander Luria belonged to this group (whose work is still insufficiently acknowledged). Their activity was documented [9, 10]. Yet again: empirical evidence undergirded a rich production of breakthrough concepts waiting to be integrated into the body of knowledge of the science of life.

These preliminary notes on anticipation are also not intended to rehash history. Rather, the historic record serves as background for identifying a first conundrum: Given the significance of epigenetics and anticipation, how come the scientific community's acceptance of these processes was so slow? Moreover, how come the foundational work, in the absence of which knowledge is reduced to the descriptive, is avoided, even by those who currently seem to be attracted by phenomena epigenetic in nature or by anticipation-based activities? In our days, there are conferences: most recent is EpiSyStem: Stem Cell epigenetics (July 2022 Milan, Italy); and Anticipation 2022 (Tempe, Arizona USA), where even the chief of the Federation of the Huni Kui people will speak (in full tribal gear). There are journals, book series, endowed chairs, and everything else that reflects the search for an academic niche by using attractive keywords. There is no difference between such headlines as "Mother Knows Best" [11]; "Epigenetics: The Sins of the Father [12]; "Grandma's Experiences Leave a Mark on Your Genes" [13]; "Sperm epigenetics and influence of environmental factors" [14]; and the subject of various funding applications (submitted to the National Science Foundation/NSF, the National Institutes of Health/NIH, or to DARPA). The same holds true for subjects regarding anticipation, which the once illustrious discipline of Future Studies is trying to integrate (to the extent of renaming itself in order to get some legitimacy). "Anticipating a Breakdown" ([15], medically reviewed by White), "Hospicing Modernity" [16], "An Impending Breakup" [17], and so on belong to productions in which the word "anticipation" is used, but unfortunately in a manner that has nothing to do with what it actually means.

That anticipation processes are definitory of the living remains almost a tabu subject. The fundamental aspect of how the possible future becomes part of anticipation action is either ignored or sacrificed for the machinist view dominated by probabilistic inference from the past. Empirical evidence is replaced by convenient data processing of probabilistic phenomena. Thus, the vicious circle of proving a false premise by generalizing from outcomes conditioned by such a premise is closed. For the sake of explaining this situation, let us examine the nature of the knowledge to be gained if an appropriate foundation is established.

2 "Knowing That" and "Knowing How" Revisited

Rejecting the "official doctrine" of' Cartesian dualism, which ascertains that the mind and body are distinct, Ryle [18] distinguished between the "knowing that" and "knowing how." His famous example is riding a bike. You don't need to study anatomy, or physiology, or physics, never mind chemistry, in order to eventually discover how to place your feet on the pedals and steer the bicycle, and to keep going if you want to maintain balance. "Knowledge that" is not, at least for Ryle's example, a condition for "knowledge how." But the majority of those who use machines—such as cars, dishwashers, iPhones, etc.—have no idea (or even wrong ideas) of how they work, i.e., have no "knowledge that," or have the wrong explanations, even against evidence. More interesting yet: enamored of measuring everything, the majority of people relying on data (from measurements) have no idea how the data—the premises upon which machines function—are harvested. This is the epistemological "Achilles Heel" of our time. It is easy to notice that in its current state, "riding the bicycle" of epigenetics or of anticipation is dominated by the "knowing how": operational knowledge as a skill, in the absence of understanding the science upon which machines are conceived and measurements are carried out. Indeed, genetic sequencing—find the order in which the four nucleotides that make up a DNA strand are connected—is the bicycle. Given the enormous investment in "measuring" the DNA—the humungous genome project—it comes as no surprise that genetics is even defined in connection to it. The underlying genetic (genotype) of cell activity (resulting in the phenotype) is important, but the "bicycle of life" depends on more than the DNA, especially more than the model currently in use (Fig. 1).

The standard (by no means unanimously accepted) definition of epigenetics is the study of heritable changes of DNA, not involving changes in a DNA sequence, that regulate gene expression [20, 21]. In respect to anticipation, the standard definition (also by no means unanimously accepted) is: a system whose current state is determined by a predicted future state [22]. It is easy to see why neither epigenetics nor anticipation research went beyond the deterministic understanding of the dynamics of the living that corresponds to the Cartesian Revolution. DNA was declared, and is actively promoted, as the blueprint of life. In other words, based on this idea, everything that the living endowed with DNA features is the expression of elements making up the double-stranded helix famously discovered by Watson

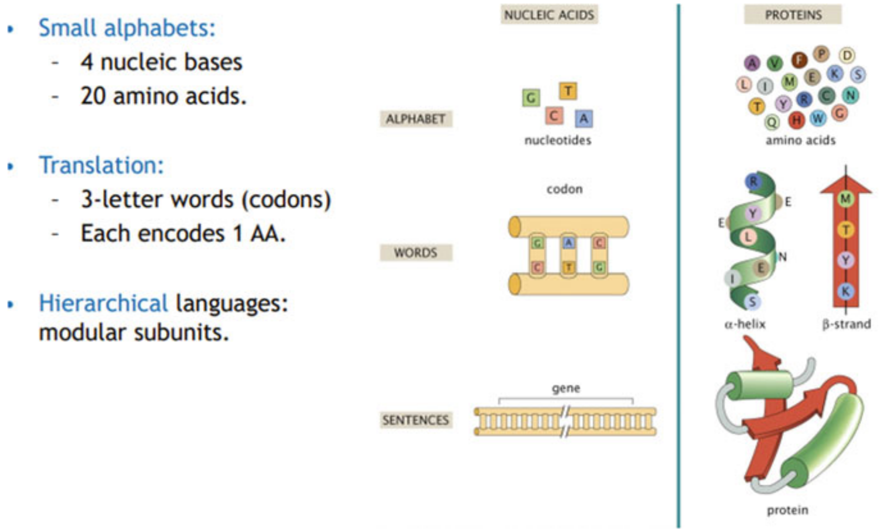

Fig. 1 Living matter theory according to Tsvi Tlusty (Lecture at the Physics Department at UNIST, [19])

and Crick. (Another individual, Rosalind Franklin, was also involved, but this is a different story.) Epigenetics is usually commissioned to prove that this is the case. Unfortunately, challenging this perspective has no place within the current genetic dogma.

A far as anticipatory processes are concerned, Rosen's exceptional contributions overshadow any ideas prior to his (his intellectual horizon was very broad, and he was aware of work done by others before his time). Moreover, those who follow in his footsteps ignore the contradiction implicit in the definition quoted above. Prediction—which his definition conjures—is antithetical to anticipation: to predict is to generalize from the cause-and-effect sequence, exactly what Rosen explicitly tried to avoid, or at least to suggest that it cannot explain anticipatory action.

The first conundrum—from low level of acceptance to forceful falsification of the epistemological premises—is not easy to overcome. Unless the scientific community takes note of the implicit limitations of faulty definitions, "knowing how" remains the only outcome, to the detriment of the ontological foundation expressed through "knowing that." It is therefore not surprising that science hostage to the Cartesian understanding of the dynamics of reality ceased to be productive, becoming a technological enterprise lacking in vision. The consequential nature of epigenetics, as well as of a science of anticipatory processes, was, so far, undermined by the confused epistemological grounding in reductionist-determinism. The learning cell is anticipatory; DNA is not. It is a stable chemical, with a double-stranded structure, incapable of learning. It is "a list of ingredients," but not a plan for action.

3 Darwin, Lamarck, and the Octopus

Darwin's *On the Origin of Species by Means of Natural Selection* [23], with its "detecting the smallest grain in the balance of fitness," projects a perspective of phenotype as the outcome of various traits: "The grain will determine which individual shall live and which shall die…." That Darwin was influenced by Jean-Baptiste de Lamarck is well known. Still, their views were deemed exclusive of each other, until Jablonka and Lamb [24] advanced the idea of a possible complementary view in the tile of their book, *Epigenetic Inheritance and Evolution. The Lamarckian Dimension.* This suggestion is relevant as we discuss Epigenetics and Anticipation because each of these knowledge domains ascertains complementarity: epigenetics to genetics, anticipation to reaction. Lamarckian inheritance and population genetics can be seen as reciprocally exclusive, or they can be seen in their unity.

To exemplify the thought, let us take a recent explanation of the self-destructive pattern of octopuses [25, 26]. The genome of the octopus comprises 33,000 protein-coding genes [27]—more than what humans have. Its evolutionary development ranges over 500 million years [29–31]. The octopus is a living creature with a large brain and an elaborate nervous system. From an evolutionary perspective, what attract attention are the eyes (which people who grew up in the age of the digital camera often describe as camera-like), the extremely flexible body, and very rapid change in color and shape. Under the scrutiny of geneticists, some [32] go as far as to question the possibility of applying to octopuses (of which there is quite a variety) localized Darwinian evolution on Earth. They advance the hypothesis of an extraterrestrial origin: "given our current knowledge of the biology of comets and their debris, the new genes and their viral drivers most likely came from space" [32, p. 12]. Be this as it may—an idea that will be either ignored or derided—it does not explain self-injuring and self-destruction in an organism often mentioned as "extremely intelligent" [33]. Empirical data (copiously shared by Wang et al. [25]), documents that post-insemination process, the male dies, while the females brood their eggs, starting what is usually called fasting, and undergoing physiological loss of function. There is what can be described as self-injury—people (scientists or not) who witnessed it are at a loss to describe this kind of behavior. Death appears not as the outcome of disease or injury (through predators), but rather as suicide—to use a term describing human behavior. First surprise: removal of the optical glands leads to a reverse path: the female octopus abandons her eggs and follows a normal path: feeding is resumed, even new mating takes place. The lifespan extension is ca. 40%, living longer than intact octopuses do.

No doubt, there is a lot to be learned about a self-destroying organism; three other aquatic animals also seem to be suicidal: salmon, dolphins, whales. However, a lot depends on the perspective of the inquiry [34]. Evidently, ending one's life is not characteristic of any physical or chemical process. There must be be life, which non-living matter does not have, in order for it to be terminated. Therefore, logically, to study the self-destruction of octopus life (or, for that matter, of dolphins, salmon,

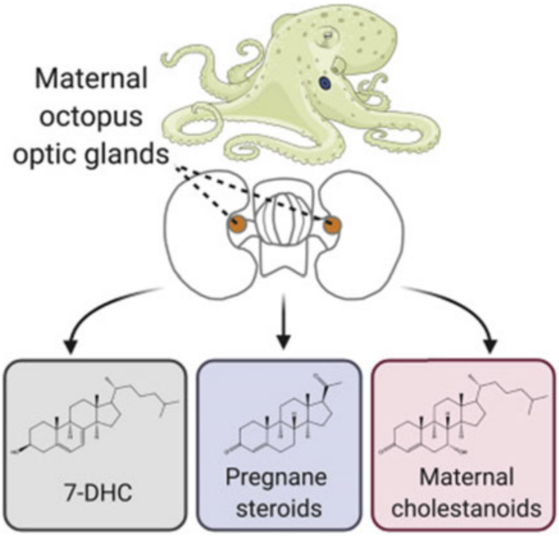

Fig. 2 This is the Graphical Abstract of the article Steroid hormones of the octopus self-destruct system, May 12, 2022, *Current Biology*. Reproduced with permission from Elsevier

starfish, and even a whale, of lemmings, bees, ants, or of human suicide; [35, 36]) has to be informed by

(a) accepting the difference between non-living matter and living matter;
(b) developing means and methods adequate to describing change (including end of life) in the living.

For the sake of argument, let us describe what was done in order to conclude that the explanation is "an imbalance between 7-DHC and cholesterol" [37] that "can dramatically alter steroidogenesis (Fig. 2).

All is based on transcriptomic findings, a molecular biology approach. Like all genetics-driven reductionism, you first kill your subject. Octopuses were bought, "animals were definitely sexed [...] females with mature ovaries, ovarian follicles, and no evidence of fertilized eggs were positively identified as unmated females. Indeed, the EU Directive 2110/63EU Guidelines on cephalopod use were strictly observed. After anesthetizing the subjects, following perfusion "the animal was decerebrated [25]."

No need to reproduce further details. Although one question cannot be avoided: Why kill them instead of collecting a specimen that died naturally? What followed is the Sanger sequencing. Not different from any and all sequencing: you take the living, kill it, and then look for the chemistry—the sequence of nucleotides in the DNA—corresponding to life phenomena in order to explain them. Genetic reductionism is a form of chemistry reductionism: find the chemical elements to be associated with a life phenomenon. It is applied to bacteria sequencing, and to animal and plant sequencing. What we learned so far about the behavior of octopuses, or for that matter about plant dynamics, or the nature of Covid-19 infection is that a formidable technology is available for producing extremely precise descriptions of the chemistry involved in life. But since there is no explanatory power in such descriptions; moreover, since what is measured might reflect the decerebration; mor than what leads to suicide, we face new questions. The conundrum of precision to the detriment of meaning becomes apparent. Data-rich and knowledge-poor is equivalent to riding Ryle's bicycle, driving your car, or piloting a private jet without understanding what they are and how they function. Worse yet: if you take them apart, there is no riding anymore. Sequencing describes in detail what they are made of but does not explain how they function. In the case of organisms, what is eliminated in the genetic sequencing is the definitory characteristic of life: its anticipatory nature. The living cell is anticipatory in its interactions with other cells (adjacent or remote); DNA is a stable chemical compound with a well-determined structure. There is no anticipatory process at the DNA level.

4 Blueprint of Life?

This is the juncture at which the legitimacy of epigenetics becomes evident. And also an instance of the unresolved conflict between those who reduce everything to the genome and those who realize that the complementary dimension defined as epigenetics is essential for understanding the dynamics of life. In particular, phenotype variability, empirically documented, raised a question impossible to ignore in view of the genetic explanation advanced so far. Does Darwin's original view, which accepted a Lamarckian model—the transmission of characteristics developed during life—explain the random germline mutations followed by natural selection on the progeny? Measuring mutation rates and mapping genotype-to-phenotype processes evinced not only the nondeterministic nature of such processes, but also the variation in their timescale [38]. Arguments used for defining the ability of organisms to adapt to changes in the environment suggest the need to define adaptive plasticity. Predator–prey cycles, climate changes (some cyclical, some not), immune system expression, and similar evince a component that belongs to the evolvable. Anticipatory processes are ahead of change. This can pertain to a short-time possible change (e.g., sexual expression before earthquakes or storms), or to long-term changes (such as geological events). There is empirical evidence for processes in which organisms "tune the timescale of their heritable variability to match the timescales of the acting selective pressure [38, p. 656]. Transgenerational epigenetics responses to environmental challenges [39] and premature attractiveness (in anticipation of non-deterministic process affecting sperm quality and other stress factors) confirm the suggestion that epigenetic interventions are often in anticipation of factors undermining the life of some organisms.

With all this in mind, we need to be aware of the fact that the dominant view is that phenotype change is mediated through changes in the DNA sequence triggered by epigenetic modifications. However, "In recent years, the belief that the genetic code is the sole basis for biological inheritance has been challenged by the discovery of trans-generational epigenetic inheritance" [40]. Environmentally induced phenotypes (persisting for generations)—due to environmental factors—are not only in reaction to natural cues or stress, but often anticipatory [41]. Immune priming in vertebrates and invertebrates is an example.

But when all is said and done, the Medawar and Medawar [42] formulation stands out: "Genetics proposes, epigenetics disposes." To exemplify, let us reference yet another success: a gene mutation, occurring rarely (below five percent of all cancer patients), diminishes the success of chemotherapy. Instead of shrinking during treatment, the tumors of these patients grow. An epigenetic intervention through Dostarlimab (a new drug) changes the situation [43]. Regarding recent attempts at understanding genetics, in particular, the "Anticipatory effects…can evolve if environments are predictable across generation" [44], the role of DNA gives this provocative formulation an even broader meaning. First came the reaction to the monetizing of genome testing: "overstating the real nature of our DNA and believing that it is more important than it is" [45]. Determining destiny and identity through DNA sequencing is a representation ingrained in our culture because scientists overstated their case, and because "spit-into-the-tube" became fashionable, and profitable—even DNA from pets is now submitted to various commercial enterprises.

Even more relevant in discussing the consequences of doing biology under the guidance of the reductionist-deterministic flag is the realization, timid as it is, that "DNA may not be the blueprint for life—just as scrambled list of ingredients." This is the title of a press release from the University of Maryland. The peer-reviewed papers are from the *Journal of the Royal Society Interface* and in *BioEssays*. Inheritance, in Antony Jose's [47, 48] model, is seen as the outcome of a process involving entities (the genome, but also other molecules in the cell), sensors that make endogenous and exogenous interactions possible), and properties (such as arrangements of a molecule, concentration, proximity, etc.). One easily recognizes the inspiration: computer science, actually the machine view of the living—yet another conundrum to be aware of: To which extent is the real (biological process) and its model (computer, or DNA, or whatever) equivalent? Better yet: To what extent is inferring from the surrogate (no longer the monkey or the mouse or the rat, but the computer model) to the dynamics of life justified? The "ingredients of a cake", i.e., "the recipe coding for thousands of proteins that interact with each other and with the environment" does not mechanically reproduce in the "real cake," i.e., in the variety of organisms, none identical with each other. Machines make identical copies; the cell makes "different" copies. That is why neither von Neumann [48], with his model of "self-reproducing automata," nor those following in his footsteps (Antony Jose is one of them) succeed in defining life and how change takes place in the living.

Epigenetics offers a cognitive path towards resolving the conundrum of confusing the real and its representation. What it convincingly proved in its recent history—still under the tutelage of genetics—is that there are many ways to bring to life the chemistry underlying change in the living. Before suggesting our own view on the matter, as it pertains to anticipatory processes and to epigenetics, let us revisit—without any claim of exhausting the subject—how epigenetic interactions affect life.

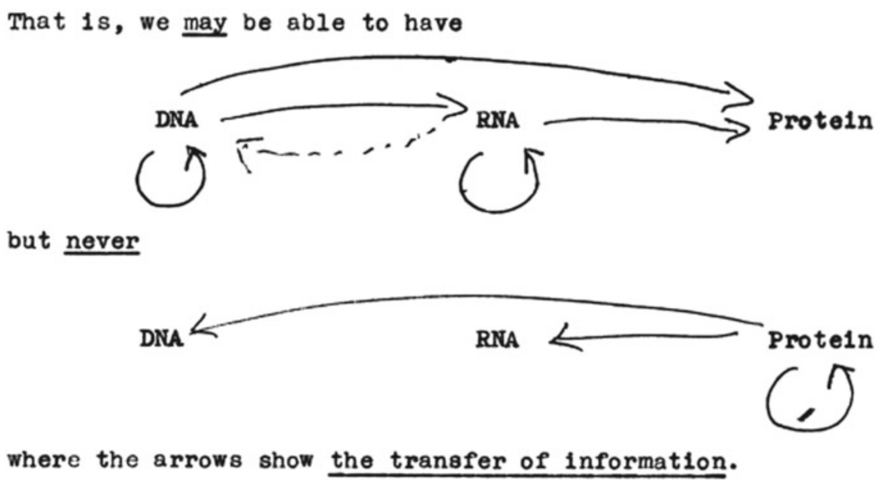

Fig. 3 Francis Crick's unpublished 1956 sketch of the central dogma (Image Wellcome Library, London)

The central dogma of biogenetics sees life as the expression of a sequence: DNA → RNA → protein (Fig. 3).

In a report on a meeting on "Frontiers in epigenetic chemical biology," Ganesan [49] takes note of the fact that "phenotype diversity of life on earth is mirrored by an equal diversity of hereditary processes at the molecular level." Even the mercurial (and often wrong) John D. Watson (co-discoverer of the DNA double helix) realized that "You can inherit something beyond the DNA sequence."

Empirical evidence shows that there are many processes that affect gene activity without changing the DNA sequence. So far, some of these seem to have stolen the limelight: methylation, acetylation, phosphorylation, ubiquitylation, sumolyation. DNA methylation (the focus of Szyf's contribution in this volume [76]) is the easiest to study with the available measurement technology (Fig. 4).

But there is also chromatic modification, and there are quite a number of other epigenetic paths. More important: in addition to matter (various substances) that can lead to changes in genetic expression, there is a rich body of accumulated evidence concerning licking, grooming, a variety of nursing paths, and many other behavioral influences. Although some are the result of observing surrogates (mice, rats, monkeys, etc.), there is enough reason to assume that humans behave similarly. And, of course, there are environmental factors, including interactions within species or among different species. Regulatory proteins, of instance, reflect nutrient availability [50]. Transcription patterns in bacteria are evidence that they anticipate environmental changes (storms, earthquakes). As cells grow and divide (the so-called cell cycle), they undergo interphases preliminary to mitosis. The new cell (daughter cell) will undergo different stages before the two copies of the genetic material (resulting from mitosis) enter into the dynamics of transgenerational epigenetic inheritance. The recent completion of the genome (annotation of the previously missing 8% of

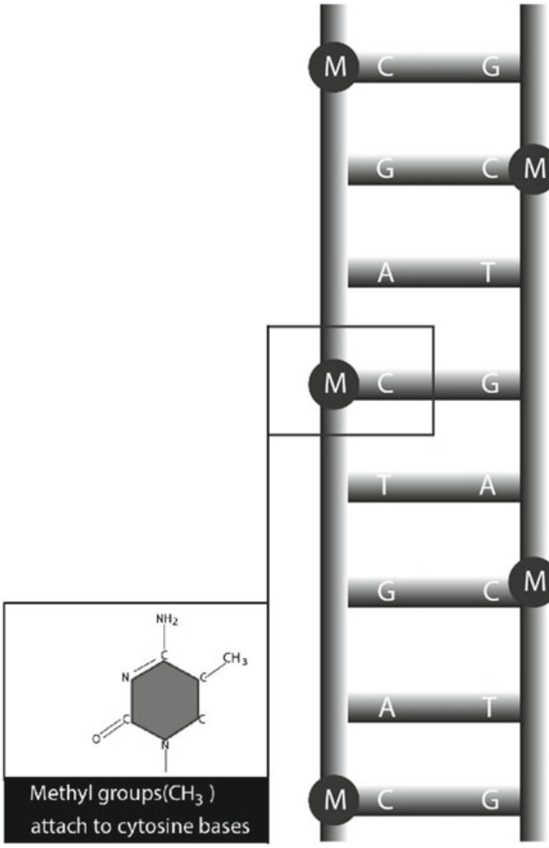

Fig. 4 DNA methylation regulates gene expression

it) provided new means for understanding epigenetic processes [51]. and made the community of researchers aware of the open questions they are trying to address. For instance, there are processes not yet identified or, even worse, attributed to factors that align with the reductionist-deterministic doctrine to the detriment of ignoring the nondeterministic nature of life processes [52, 53]. Given the various timing involved in genetic processes, it is probably justified to assume that the genome project will never be concluded since it is an open-ended evolving entity. To know the human is to understand its never-ending change—even though in the current view the DNA seems pretty stable. But who knows what two, three, four generations in the future will bring with them?

These preliminary considerations are the result of identifying conundrums waiting to be addressed. They are an argument in favor of providing an alternative path to understanding epigenetics and to connect it to anticipatory processes that constitute the necessary condition for change in the living. In short, foundational work, which the "know how" cannot provide, is not a luxury, but a necessity if we want to make "know that" the premise for actionable knowledge.

5 Change—The Anticipatory Condition of Epigenetic Processes

The National Library of Medicine (NLM) at the US National Institutes of Health (NIH) makes available on PubMed Central, a free full-text archive of biomedical and life sciences journal literature. Searching for keywords (single, or for more elaborate descriptions) affords an attractive meta-perspective. The titles (Who can read everything given that the curve of increasing publications is steep?) suggest that both *anticipation* and *epigenetics* are often associated with change. Weinhold [54] frames his examination of "a wide variety of illnesses, behaviors, and other health indicators" from the perspective of changes in gene functions by emphatically ascertaining "Epigenetics: The Science of Change." His list of health indicators is broad: "cancers of almost all types, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral illnesses." What follows is even more indicative of the almost open-ended kinds of processes involved:

> Known or suspected drivers behind epigenetic processes include many agents…heavy metals, pesticides, diesel exhaust, tobacco smoke, polycyclic aromatic hydrocarbons, hormones, radioactivity, viruses, bacteria, and basic nutrients.

From a cognitive perspective, it helps to distinguish between reactions (to substances, to stress of all kinds, to danger, etc.)—for which we have descriptions in the language of physics and chemistry—and anticipatory actions (such as the immune response, or any method of prevention such as a healthy diet and physical exercise,). What they have in common is that they are the expression of life. Since epigenetics and anticipatory processes share in the way they manifest themselves, what follows is an attempt to frame the subject within a conceptual foundation for a science of change. If successful, it could constitute a premise for advancing the agenda of a science that integrates reaction (deterministic in nature) and anticipation (non-deterministic in nature). Such a research perspective benefits from both the reductionist experiment (focused on the make-up of matter, atoms, molecules, genes, etc.) and the holistic (focused on the open-ended timeline of life processes, i.e., narration of life).

Axiom 1
All there is is the outcome of change.

Regardless of the viewpoint adopted regarding the beginnings of life on Earth (or in the Universe), it is clear that our very existence, as observers of reality (including our own), is the outcome of change. The most recent hypotheses are yet other attempts to transcend the "primordial soup" of life model (mix the right elements and provide an environment propitious to their combining). The claim is that it all started with the RNA–nucleoside triphosphates percolate through basaltic glass [55]. Whether this idea will withstand further examination or not, it aligns with the Axiom articulated above. Change is the origin of all there is.

In describing change, based on observations that can range between the casual, the experimental, or the empirical, what becomes apparent is that.

Lemma 1
Change can be necessary or contingent.

Just to build upon the RNA hypothesis regarding the first genetic material: the percolation in question is deterministic. Moreover, it can be only contingent since there is no necessity to its happening. The degree of the necessity of change and the nature of change (deterministic or non-deterministic) correspond to the fundamental condition of the matter in which the changing entity is embodied: living or non-living.

The WHY? of change regardless of its nature—i.e., including the emergence of life on Earth—is straightforward: interactions. The meaning of the word *interaction*: the way in which everything that exists influences each other, at all levels of their existence. This pertains to all that there is: lifeless matter (the non-living) and the living embodied in matter. Interaction and causality are of a different condition. Interactions between two entities or among several entities take place in in a never-ending back-and-forth of energy exchange. Within the deterministic model, causes are described through one-way arrows pointing to effects. They are also indicative of the order in the sequence: intervals between cause and effect are called time. This is, of course, a misnomer. Time is different from the interval between successive events. It is in fact more the rhythm in which change takes place—sometimes slower, sometimes faster. In the science grounded on measurements—always the same—intervals between measurements are also confounded with time. The consequence is evident: machines for counting intervals, such as the clock, effectively replace time. When Einstein described the space–time curving, his theory is not about intervals or distances. "What's the time?"—the usual question of the age when clocks were not as abundant as computers are today—actually meant "What interval was measured" in reference to an arbitrary beginning of the day, or the hour. This is inconsequential in respect to the non-living, where there is no birth and no death to reference to the arbitrary record of duration. However, it cannot be ignored in defining lived time—behind which age, disease, and death hide—as change of a nature different from that of the non-living. Interactions are variable in intensity and quality, as well as in their rhythm (some are faster, some are slower, some are continuous, some are granular). Causes can be sequential in nature: one, or many, after the other; or they can be configurational; or simultaneous.

The WHY? of interactions has its origin in the integrated nature of all that there is. In particular, matter and energy, which make up everything, are interlocked in the identity of all that there is, as well as in all that will be. For an observer, the relative morphological stability, i.e., the form, of things at all levels of their existence is the immediate consequence of the intertwining of matter and energy.[1] Of course, the relative stability of the form of a stone is fundamentally different from that of

[1] Physics developed the theory of forces (e.g., gravity, electromagnetism, strong, weak) in order to explain this.

a particular organism (whose form changes between conception, birth, and death), and from that of a species.

The complementarity of living matter and non-living matter is reflected in the attempt to describe through entropy the decay of non-living matter, in contra-distinction to acknowledging the diminished entropy of living matter. Without probing here in depth the neg-entropic aspect of living matter, we can provide the empirical evidence: organisms are the phylogenetic memory of the process through which simpler life forms continuously evolve. They create themselves through interactions that do not simply reproduce the previous simple form, but actually contribute to their remaking as "more" (different) than what their precursors were. The distinction (living/non-living) is different in kind from the complementarity of light as wave and particle—advanced and demonstrated within a quantum mechanics view. The view of the electron as particle and wave, or of genetics and epigenetics, or of reaction and anticipation only exemplifies Niels Bohr's concept of complementarity, advanced as a characteristic of all there is. The interlocking of energy and matter explains the stable shape of a rock (what holds all the elements in place in a particular manner); fluids taking the form of a vessel; and gases filling a room. Birds of a feather, or sheep of a flock, or zebras of the same stripe, blades of grass, fish in a school are examples that can be understood only within the evolutionary process that characterizes the dynamics of life. The question of whether qualia—ideas, emotions, feelings, and all that is associated with this label—can be identified as well through the interlocking of matter and energy could be addressed only on account of an understanding of the specific interactions that define the living. That they are outcomes of specific interactions is the consequence of the first axiom.

Axiom 2
Self-preservation of life is instantiated in its change.

As a self-organized system, the living maintains its own interlocking of matter—living (cells, for example, or neurons) and non-living matter (such as the chemicals of the DNA)—and energy through metabolism. Moreover, it maintains the integrity of its instantiation in a particular form of life (the individual animal, plant, insect, bacterium) through self-repair, for which metabolism delivers matter and energy. Robert Rosen [56] tried to capture the process as he focused on the question "What is life?" In the formalism of the (M,R) systems, Rosen demonstrated that metabolism and self-repair are closed to efficient cause, which means that they are triggered from inside the living.

Metabolism and self-repair are the particular expressions of biological matter and energy interlocked over a limited viability domain that defines life. This is self-preservation. The description of the process (i.e., Axiom 2) is the pendant to the laws of conservation of mater and energy. It aligns with the discovery of the dual nature of light and, for that matter, of the electron. And extends to genetics and epigenetics.

> The living, as a subset of all that there is—according to von Neumann, given its negentropic nature it has to be preponderant in the reality-- is self-preserving of its individuality, and of its condition of being alive. Experimental evidence confirming the empirical basis of this pronouncement continues to accumulate [57]

The pendant to the law of energy conservation is the expression of matter and energy interlocked (for instance, in metabolism and self-repair) over a limited viability domain that defines life. This thought is as significant as the dual nature of light or of the electron. It takes its particular form in the relation between the genome and epigenetic factors of all kinds. Evidently, evolving from simple to more elaborate forms, the living does not contain instructions for how to do that. It cannot be preprogramed, as machines can be. To assume that the DNA is a blueprint is to ignore the creative nature of life: reproduction at higher levels of self-organization and with increasing interaction capabilities. Outside the viability domain, the living becomes lifeless matter, while often hosting the life of other species. In death, its dynamics is reduced to that of the non-living in which all change processes are triggered from outside (the physical forces). The viability domain is that of life making and remaking itself (self-creativity) through interactions supported by metabolism and self-repair. The interlocked matter and energy, in which the living is dynamically expressed, is the unity between sameness (birds of a feather, etc.) and difference (change over time, e.g., aging). The living undergoes transformation processes through which life is continuously re-created. Although metabolism and self-repair originate from inside (the dynamics of the living is endogenous), they are subject to interactions with the outside (exogenous) world.

The non-living manifests itself in its immediateness: the here-and-now of cause-and-effect interactions change due to actions from outside. The living, on account of self-preservation, extends from the immediate to the subsequent. This is where duration, as a particular expression of time, but not to be confused with it, emerges. Interactions characteristic of the living are several orders of magnitude more diverse, and of higher impact, than those defining the change of lifeless matter. Properties of lifeless matter are defined from the elementary particles making up the matter and energy processes involved in maintaining such properties. This is a bottom-up process—interactions (endogenous) among fermions, quarks, leptons, bosons, etc. to atoms and molecules, to physical entities (such as elements and things made from elements). Interactions with the world (exogenous)—some linear in nature, others non-linear—affect their properties, as well. The particular matter-energy interlock changes under their action (metals oxidates, stones crack, water acidifies, etc.). The description of their motion (trajectory, speed, continuity, etc.) is one possible manner, chosen by physics, to characterize change (relative position to each other). Descriptions of motion—such as those facilitated by the mathematical language of analysis—are actually an incomplete record of their change: the stone wearing down into sand, for instance, without changing its position in space; or, to recall the hypothesis of the RNA as the beginning of life, nucleoside triphosphates percolating through basalt glass (Fig. 5).

Properties of living matter result from complementary bottom-up—from the material make-up (electrons, atoms, molecules)—and top-down processes—from the cell down to its various components, from the brain to the genes. Even though the living is closed to efficient cause—that is, it changes due to its own dynamics—outside forces affect it as well, since life is embodied in matter (some alive, such as cells and neurons, some not living, such as the acids making up the DNA). Energy—endlessly

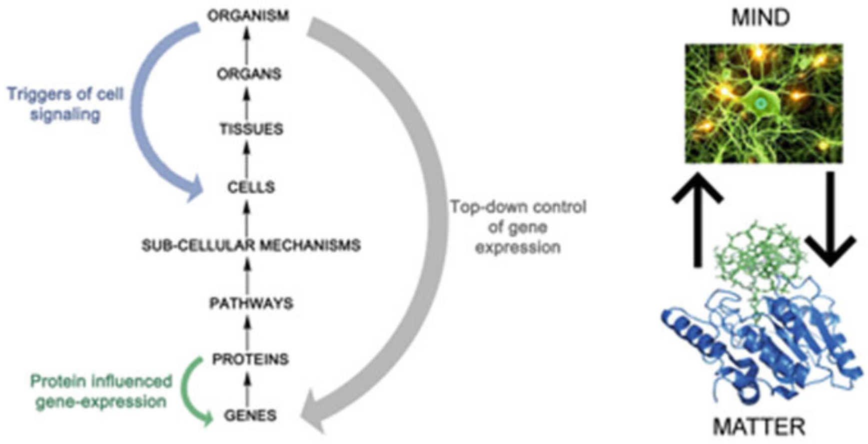

Fig. 5 Ellis [58] discussing top-down causation (cf. Interface Focus 2011)

transformed in intractable processes, but never created—is at work in affecting how matter supports (or sometimes undermines) life within the viability domain. Descriptions of motion, of things in the environment or of entities at the micro- or macro-scale (the domain of astrophysics), are relevant to physical entities. They are, however, of secondary significance in describing change in life: plants, for instance, don't literally move, although they can change their position. Ontogeny and phylogeny, as biological processes reflecting the dynamics of energy-matter interlocking, constitute specific behavioral patterns, as much as they define through, and are defined by, the material and energy make-up, in continuous renewal.

The never-ending change of any and all living entities—from insemination to birth to death—entails *creative processes.* Reproduction (sexual or asexual) is, from among a large variety of creative processes, the most prominent. To create is to make the past (what was, the genetics) and the present (what is) become a possible future (what might be). For this, perception of the future, i.e., a "sense" of what might happen, informed by, but not reducible to, sensorial perception and the rich cognitive activity this triggers, is a condition *sine qua non.* The human DNA is by some order of magnitude (25%-35%) less than that of some flowers. The immediate explanation: The "sense" of the subsequent—less defined for flowers than for humans or vertebrates—from which future is made up, is *anticipation.* Epigenetic interactions are often anticipatory. Anticipatory action orchestrates biological expression (such as motoric expression or neuronal activity) consonant with life self-preservation. The action, guided by anticipation—to which learning contributes meaning—transcends the action-reaction mode of lifeless matter—where meaning does not exist. In anticipatory action, *what is* becomes something that never existed before. Therefore, it can be qualified as creative. Flowers are "more" the same ("more" being a fuzzy qualifier) than humans are. In contradistinction to change in lifeless matter, which is essentially deterministic, anticipation-driven change is non-deterministic. It can be successful—creativity as self-preservation ("art of surviving")—or not. The self-destruct behavior pattern of octopuses (an example we dwelled upon) invites an effort to understand the drive to live and give birth, and the realization of life cycles: beginnings and ends. No awareness is involved, rather, the interlocking of life-preserving factors. Some scientists speculate that the self-destruct action—many other species are known for similar patterns—is purposeful: to provide offspring with what they need to make it, or to protect others (aging termites protecting the "community," [59]).

Lemma 2

Anticipation processes underlie evolution.

The WHY? of evolution cannot be answered without understanding that it is grounded in anticipation. From the initial life forms on record to the current stage of life on earth, the vector of change is from the simple (distinct from the non-living in which it resides) to rather elaborate (changing itself and the world in which it acts). Self-preservation guides variation and selection, from the cellular level to that of species. It succeeds to the extent to which anticipatory processes lead to successful action. The WHY? of anticipation is straightforward: there is evolutionary change since anticipatory processes (as choices made) guide interactions beneficial to self-preservation of life. Being by nature non-deterministic, such processes do not prevent species extinction.

Lemma 3

There is anticipation because there is learning.

First a negative proof: If life were genetically predetermined ("programmed"), as reductionist-determinists ascertain, there would be no need for learning. Those who maintain that the DNA is the blueprint of life might argue that the living is "programmed" to learn. This would imply a teleological dimension: learning as final cause. And it would suggest that the medium—a non-living entity made of four chemical bases structured in a sequence arranged in two long strands making up a double helix—is the message. The wrong metaphor of genetic language leads to contradictions. Learning and protein production correspond to unrelated aspects of life: learning is necessary; protein creation, in which folding, a non-deterministic process is essential, is contingent. There is no lie without protein, but the folding is not predefined. The building blocks of proteins—the 20 amino acids specified by the three bases of the DNA (codons)—correspond to the syntax of life. Learning is pragmatic in nature, at a level where communication (inside and outside the organism) is established with the purpose of maintaining and perfecting life. There is no change at the genetic level; the DNA is what it is: elements in a fixed configuration. Learning, which is an epigenetic intervention, brings life into the DNA. The dynamics of life is the outcome of learning interactions.

Change in living matter is experiential. It leaves traces that eventually form knowledge—no matter how limited—of self and of the world in which the living unfolds. The WHY? of learning is subsumed in that of anticipation—ahead of the possible, of the contingent.

Anticipatory action takes place through biophysical and biochemical processes. Such processes are not reducible to the physical and chemical processes characteristic of lifeless matter. Lifeless matter and living matter are made of elements. However, molecules of life (proteins, carbohydrates, lipids, nucleic acids) are 96% composed of only six elements (carbon, hydrogen, oxygen, nitrogen, phosphorus, sulphur). The nature of interactions that each makes possible, moreover necessary, in order to ensure self-preservation of life, defines them as different from non-living molecules. Anticipation has an existential condition (cf. the WHY? of anticipation); that is, it is ontologically defined, not epistemologically constructed. Life self-preservation is accomplished through anticipatory processes bridging the now with the immediate or remote subsequent, i.e., the possible future. The same can be said about epigenetic processes. Epi-genesis is not a construct used to explain genetic expression, but rather a very rich ever-expanding set of interactions affecting gene expression (sometimes beneficial to life, other times detrimental—cf. the octopus self-destruct behavior discussed previously).

6 The Observables of Epigenetic Expression and Anticipatory Action

The understanding of change—the epistemology—conjures constructs such as time and space. However, as we shall find out, time and space pertinent to change in non-living matter is different in nature from the time and space of life. Within a unified systems perspective, the focus is on evaluation of observables over states of the system. As Einstein remarked, and as science shows, those who define the observables control the theory. This is evident when we compare the observables in Galileo's mechanics, in Newton 's physics, in relativity theory, and in quantum mechanics None of these apply to life. They describe the reality of a non-living universe. By extension, when von Neumann [48] submitted the model of self-reproducing automata, he took the cue from the self-reproducing living. Discarding the unrepeatability of life processes, he conceived of a mathematics that affords self-making—applied in our days to robots and other kinds of machines. His observables correspond to Turing machines, and thus contribute to making a mathematical construct the prototype of the digital algorithmic computation of those days. Not unexpectedly, the "chemists of life"—biochemistry—took a ride on the same bandwagon. They produced an explanation of self-reproduction focused on the DNA, or, by extension, on genetics. In every situation, observables are the outcome of simplification: a reduction. Since the complexity of life evades full and consistent descriptions (i.e., G-complexity [60]), reductionists explain life from a particular perspective (Fig. 6).

In the non-living, mapping from states to numbers captures the nature of change. Indeed, this change (the entropy of matter) is quantitative in nature. In the living, the mapping to numbers incompletely describes the nature of change, especially in view of the fact that the observables (making up the phase space) continuously change

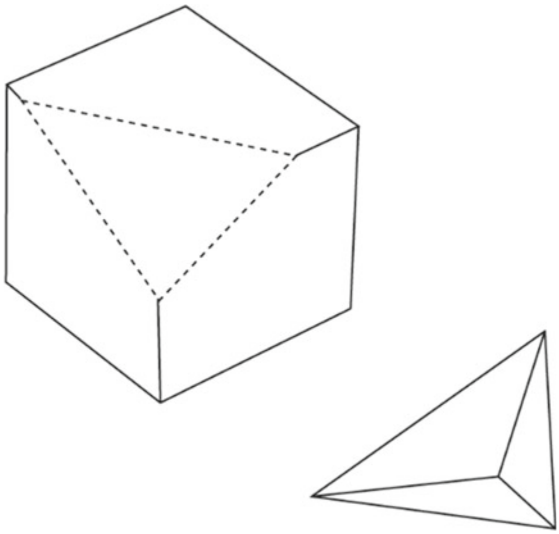

Fig. 6 The epistemological cut—selecting a limited aspect that can be fully and consistently described

[52]. To better account for the change in the living, it becomes necessary to perform mappings from states to meaning—their significance for the living process—as it applies to the self-preservation of life. Epigenetic interventions of material nature (e.g., use of drugs, such as in the treatment of rectal cancer, as mentioned above; [43] or any other form of interaction (spiritual influence, ecological factors, etc.) can be associated with genetic processes but are not reducible to them. They take place over time. Therefore, to understand them, sequences of maps must be generated, that is, a film sequence of the process subject to inquiry from the perspective of how each step (in the time series) is significant for the self-preservation of life. It is not enough to identify one or another process (methylation or chromatin modification) in the absence of the larger context. Just as an example: imprinting.[2] If one of the two alleles of a gene pair is "silenced" due to an epigenetic process, the allele expressed might be vulnerable (to microbes, or some toxin). Genes that can be imprinted are subject identification given the vulnerabilities associated with the process (Fig. 7).

In the reactive system of the non-living interactions, the state of the system depends on its past:

$$\mathrm{x(t)} = f(\mathrm{x(t-1)}). \tag{1}$$

Therefore, the description of the dynamics of lifeless matter is straightforward: its change is fully described through the variables relating the past to the present (characterized as duration and proximity). The number and variety of parameters describing the non-living is finite (even though it can be very large). Interactions in

[2] Imprinting: a rapid learning process that takes place early in the life of a social animal (such as a goose) and establishes a behavior pattern (such as recognition of and attraction to its own kind or a substitute). (Merriam-Webster).

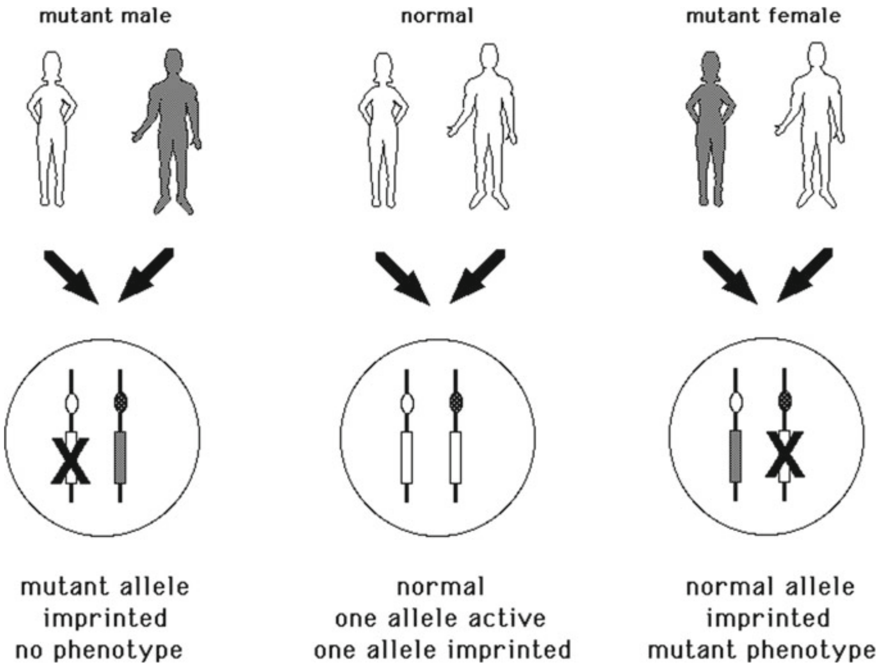

Fig. 7 Genes imprinted

lifeless matter and among non-living entities is described in the dynamics of action-reaction, i.e., deterministic causality (including, for instance, processes described in chaos theory, the mathematics of dynamic systems). Inferences from parts to the whole are possible because interactions through which matter and energy are interlocked are preserved (up to a certain scale). Variations (an expression of our imperfect descriptions) appear to average out. As part of the organism, the non-living, such as the DNA and genetic processes associated with it, can be measured—that is what sequencing, the dominant measuring process of our time, does. The deterministic machine called *compute*r provides the high analytic performance expected once the data reach a very high scale.

Living systems are anticipatory. The current state of an anticipatory system depends on past, current, and possible future states:

$$x(t) = f(x(t-1), x(t), x(t+1)) \tag{2}$$

The dynamics of the living cannot be described and explained without considering the possible future. DNA is blind to the future. It encapsulates past and, at most, might undergo accidents. The number of variables describing the dynamics of the living is as open-ended as the possible future-based choices it faces as it unfolds over its viability interval. The interlocking of energy and matter in the living makes

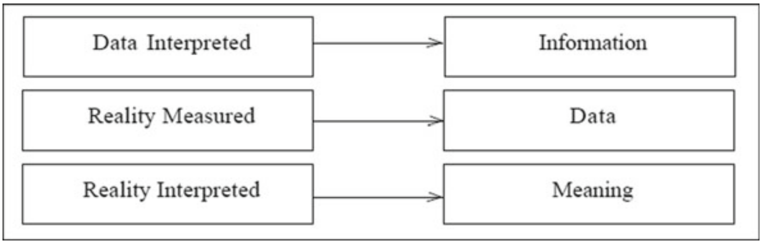

Fig. 8 Data: matter/meaning: life

possible the simultaneous condition of sameness (in species, in offspring) and difference (expressed as individuality, of which lifeless matter has none). Inferences from parts to the whole in the living are at best misleading. Interactions through which living matter and energy are interlocked is specific to each and every life level: cells, membranes, tissues, organisms, etc. Lifeless matter is homogenous—atoms, molecules, chemical elements, are each of the same nature. All electrons are the same. The elements have a specific composition that defines their identity (e.g., oxygen or hydrogen, copper or uranium). Life embodied in matter is heterogenous from the cell level to tissues, to organs, up to the organism. The identical is an identifier absent from anything living.

Lifeless matter neither reproduces nor replicates itself. Life self-preserves itself through replication, involving genetic elements (such as DNA molecules), but not limited to their chemistry. Reproduction is actually No-reproduction, but diversification. Intertwined sameness (of species) and difference (of individual organisms) correspond to creative change: life is always made from life, continued in never-repeated forms. Paradoxically: the pattern of no-pattern (Fig. 8).

Time and space, in the living are not a given stage on which things happen. Rather, they are the outcome of change, coextensive to change.

- Lifeless matter is describable through measurement/quantity, number, math—subject to falsification
- Life is describable through meaningful time series (narrations)—ambiguous.

To know (as in riding a bicycle, or carrying out genetic sequencing) is to experience HOW? *To know that* (i.e., what makes the action possible) is to understand WHY? [18]. In this respect, the study of the octopus's self-destruct behavior is perfectly justified. But the results depend on the perspective, i.e., the measurement means and methods. The killing of the organism as a preliminary to finding out why the living specimen behaves in some peculiar (to humans) manner diminishes the choice of observables. Of course, genetic sequencing will output what genetics is about: chemistry. But the behavior in question is different in nature from chemical reactions. It corresponds to interactions with other species (availability of sustenance), as well as with the environment. Does the octopus mother, without any explicit awareness of the possible future, sacrifice herself for the sake of the offspring? The notion of sacrifice corresponds to an anthropomorphic perspective: explain what is done in

Nature by assuming that it behaves like humans do. But the answer afforded via chemistry is also anthropomorphic: it must be steroidogenesis. Actually, genetic sequencing, unveiling the syntax of genetic processing, could not address questions pertinent to "know that."

Axiom 3
"Knowing that" is not experiential.

To know that (for instance, how epigenetic processes affect DNA expression) and to account for how "knowing that" changes the knowing subject is at the core of Popper's criterion of falsifiability [61]. Most knowledge in the living is implicit. It is expressed in the change experienced and results in changed patterns of behavior, i.e., in new forms of interaction. The WHY? question is irrelevant for the experienced. You bike without ever contemplating the WHY? question. For that matter, we live without knowing what life is. The human being observing change in nature is inclined to attribute a human dimension (anthropomorphizing, as explained above) to such change. The extreme reaction to this epistemological trap (we see ourselves in what we observe) is the attempt to create a context in which measurement replaces impression. In time, quite a number of means and methods for measuring have been conceived. The history of science documents such advances. What if it fails to do is what some scientists, fully dedicated to the knowledge domain they are active in, eventually realize. In his Nobel Prize acceptance speech, Albert Szent-György (Laureate in Physiology or Medicine, 1937) provides a good illustration of the thought:

> As scientists attempt to understand a living system, they move down from dimension to dimension, from one level of complexity to the next lower level. I followed this course in my own studies. I went from anatomy to the study of tissues, then to electron microscopy and chemistry, and finally to quantum mechanics. This downward journey through the scale of dimensions has its irony, for in my search for the secret of life, I ended up with atoms and electrons, which have no life at all. Somewhere along the line life has run out through my fingers. So, in my old age, I am now retracing my steps, trying to fight my way back.

This is extremely relevant in the context in which the observables—what we measure—change.

Let us recall examples from behavioral epigenetics. How change affects experience is reflected in the changed behavior. Behavioral epigenetics is illustrated by examples ranging from the individuals who were prenatally exposed to famine during the Dutch Hunger Winter to the offspring of Holocaust survivors. To understand change implies awareness of consequences: the children of the Dutch Hunger Winter of 1944–45 had, six decades later, less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings [62]. Of course, what is observed, i.e., measured, is different from what actually took place. Not surprisingly, there are scientists captive to measurement who dispute the findings related to the Dutch Hunger Winter or to the Holocaust survivors because genetic inferences taken out of the context of life are ambiguous by necessity. Beyond controversy is the need to understand living processes in a holistic context. Learning, as the multitude of processes through which holistic anticipatory processes are informed, is expressed in accumulated understandings that pre-empt undesired experiences.

Being the axiom of life, self-preservation becomes by necessity the criterion for qualifying changes pertinent to the living: undesirable, creative, inconsequential. To know something has the immediateness of experiencing it and the subsequent action it informs.

To understand is by necessity an activity involving the change under inquiry, the inquiring subject, and all mediating entities between the two. To know how the change of lifeless matter affects the self-preservation of life is to form a representation of the possible interactions between them.

7 The Threshold of Complexity

The above-formulated axioms are premised on rich empirical evidence, as well as on experimental outcomes, including negative results (respectively, failed anticipation and epigenetic expression to the detriment of life) and failed replicability (discussed in [52]). What follows is an attempt to elaborate on the pronouncements within a method co-substantive with the subject. David Deutsch (*The Beginning of Infinity*, 2011) correctly described succeeding theories: Galileo's *Dialogue Concerning the Two Chief World Systems*, 1632; Newton's *Philosophiæ Naturalis Principia Mathematica*, 1687; Einstein's *On a Heuristic Viewpoint Concerning the Production and Transformation of Light*, 1905; and quantum mechanics. Of course, the correspondence principle holds: Galileo's mechanics is right—i.e., can be used and tested—until the moving objects are characterized by their mass, and therefore their interaction cannot be ignored; Newtons' mechanics (describing particular gravity-based interactions of non-living bodies) is right until the speed of movement comes close to that of light; Einstein's physics is right until Heisenberg's uncertainty principle (i.e., the quantum mechanics view) comes into play.

But each new paradigm—a breakthrough at the time it was articulated—ascertains discontinuity also: the mechanics of falling bodies (Galileo) is of local significance. Newton's view according to which the universe obeys the same laws of Nature introduces gravity as a force exerted upon interacting bodies; in Einstein's universe, there is no place for such a force: Earth's mass causes space–time to curve. In this distorted space–time, the shortest path (the geodesic) is no longer on a flat surface (plane), but on a sphere. Einstein's view on the limited speed of light is, in turn, challenged by the instantaneous entanglement of photons (which led him to write about "spukhafte Fernwirkung"—spooky action at a distance).

It is quite possible that anticipation, as definitory of the living, will prove to be a breakthrough, after centuries in which biological subjects have been explored from the perspective of physics and chemistry. The correspondence principle will have to be rewritten: the biological, above the threshold of complexity at which decidability is expected, seems to ascertain a view in which the physical is the particular case. Indeed, within the reductionist-deterministic premise of explaining the world, the living has been a particular case, a subset of physics, or of the physio-chemical model of reality. The life sciences have operated under this assumption, and consequently, biology was corralled into biophysics and biochemistry. Given that life is non-decidable (for arguments, see [60])—i.e., as opposed to the non-living, it cannot be fully and consistently described—it follows that below the threshold of life, causality is by many orders of magnitude below that characteristic of life processes. Consider only the fact that genetics expression, focused on DNA, with its large data description, is much simpler than epigenetic interaction, and you have a vivid image of what the particular case is, and what the encompassing nature of life is. After all, the living can produce non-living entities; the inverse does not hold.

The most important consequence of this epistemological understanding is that change—and its causes—is key to efficiently distinguishing between biology and physics or chemistry. At this juncture, it becomes clear that science has reached, through the proper understanding of the living, a level of generality impossible within the focus on particles, atoms, molecules, etc., or chemical components such as DNA. Therefore, one cannot continue promoting the language of Descartes—who built upon Plato's "nothing can come without a cause" (*Timaeus*)—in addressing something that Descartes' axiom excluded: a cause that lies in the possible future. Einstein's message—"No problem can be solved from the same consciousness that created it. We must learn to see the world anew."—is in this sense more current than ever and pertains to anticipatory processes as well as to epigenetics. It makes little sense to couch anticipation within conceptions anchored in the past—or to legitimize it, in a castrated rendition within which the future is the outcome of probabilistic evaluation, within modes of arguments contrary to its condition. Once again: the same holds true for epigenetics, especially for couching it in genetics, and its surrender to the measurement technology associated with the genome.

8 Distinctions

To learn about the world is to learn about its change. Explanations of change within the physics-dominated understanding of the world or within the chemistry of genetics characterize only a small part of the dynamics of life. They return partial descriptions of non-living matter, leaving out what characterizes life. The very idea that change is of essence goes back to Heraclitus, who maintained that fire was the cause of change. If fire is understood as energy, we are not far from what science ascertains in our days. This idea is not contradicted within any conception of lifeless matter (physics, chemistry). Its relevance becomes clear when examining living matter, i.e., organisms. Anticipatory processes, in particular in the form of epigenetically triggered genetic functions, underlie change under the axiom of self-preservation of life. Obviously, as living observers learn about how things (living or not) change, they are subject to change as well. The circular nature of knowledge acquisition is significant because even in the conversation on the nature of who we are and what defines us, epigenetic influence is exercised. There is a continuous feedback cycle, resulting in phenomena ranging from self-delusion (superstition and mysticism are examples) to self-motivation. Let us recall testimonies regarding a patient's will to live and how it affects the outcome of medical care. Such examples are not reproducible because they testify to the uniqueness of each person. But that would be a subject in itself. Change takes place on account of interactions among all that there is. Associated with this fundamental premise is the axiom of existence. All that there is—material or of a different nature (such as emotions, thoughts, cognitive constructs, etc.—is the outcome of change and becomes the locus of future change. In even simpler terms: regardless of the views one holds about the beginning of the universe, not to say the beginning of life or of humanity, even beginnings are the outcome of change leading to subsequent changes.

There is no place in this view for anything that would qualify as nothingness because interaction implies distinctions. Change multiplies distinctions. If it leveled them, it would outcome nothingness corresponding to absence not only of matter, but also of energy. From all the knowledge acquired so far, energy is subject to transformation, but not to exhaustion (into nothingness), and even less to self-generation.

It does not take sophisticated experiments to find out that change of lifeless matter and change of the living afford different perceptions under observation. A stone changes over time, as weather changes, or as it interacts with the living: seeds finding a niche in the smallest crack, all kinds of life forms seeking refuge near it, the chemical reactions between its constitutive elements and acids (in rain, urine, feces, etc.). All these can be measured, and are measured more and more, since measuring methods and measuring devices are continuously developed for this purpose. The data acquired represent various aspects of the change. The assumption of a complete description corresponds to the nature of the described (i.e., the stone in this case). To observe a newborn (a hatchling from an egg, a faun from a doe's womb, a plant from a seed) could also inspire measurement. Books were written that detail the apparatus for measuring what an egg is, what it is made of, how fecundation affects it, etc. Let's recall Aristotle's contribution to science demonstrated by his classic empirical observation of the growth of a chick inside an egg. There is no data, there is a record of change ("the film," the narration). The fanatics of measuring still seem unaware that numbers do not provide access to the creative dimension of change, i.e., how something that never existed comes into existence. Embryonic stem cells in interaction with fibroblast growth factors (FGFs) are primed to become a goldfinch, but not a copy of any existing one, rather a unique bird never yet encountered. This is where the anticipatory nature of epigenetic processes becomes evident. As already pointed out, the assumption of a complete description, under which genetics operates, is not realistic since the number of observables involved in the process changes as well.

We shall see what it takes to understand the difference between change in lifeless matter and in the living as we advance in defining the perspective from which such an understanding becomes possible. Let's take note of the fact that in this world of inexhaustible change, the understanding of the observers themselves, of who they are and how they take in the world to which we belong has changed over time.

Let's take one example: A large variety of eyes—on fish, butterflies, owls, octopuses, etc.—testifies to ways in which the living learned to see the world, and thus overcame the limits of only reacting to it. (Of course, the other senses were involved as well.) Dated in the Cambrian period, during which evolution seems to have known an accentuated dynamic, the eyes affected adaptations, and were affected by them. What today we call visual acuity, sensitivity, motion resolution, and color distinction were and are shaped by the environments in which organisms live. This is the answer to the WHY? Of such characteristics of vision. None other than Darwin suggested a progression from "an optic nerve" to what eventually became, in vertebrate evolution, a patch of photo receptors [63]. Empirical evidence, of the nature of Aristotle's observations of egg germination, suggests that evolution in itself is beneficially influenced by higher light sensitivity. Molecular biology made possible the retracing of the co-option of a protein from some other function to the formation of photosensitive cells. Genetic mechanisms were identified [64] in respect to the location of eyes in organisms as diverse as octopuses, mice, and fruit flies.

Most significant from the perspective pursued here is the fact that interactions with the world, enabled by sensory organs, are from early on not reduced to reaction. Light, of course, would lead to a response (defined in the context of interaction); this corresponds to the cause-and-effect physics of reaction. But seeking light, or for that matter, darkness (e.g., in order to avoid danger, to find a moist area where nourishment might be available) is anticipatory. This exemplifies a concrete path of life self-preservation dynamics. The light-sensitive protein opsin and the molecule facilitating color distinction make up the photo receptor cell (eyespot). Organisms of different species and types do not see the same image of an object within an environment. They distinguish *Umgebung* (the universe in which they live) in the self-preservation environment—*Umwelt*, as von Uexküll [65] called it. In some cases, the sensorial representation is transmitted to the brain (when e.g., sustaining circadian rhythm); in others, the sensorial guides action (reaction or anticipatory action). Cladonema (a sort of jellyfish) has no brain; the eyes seem to control the motoric directly. Molecular biology helps in understanding the intricate nature of what we take for granted when referring to the sensorial.

These minimal notes (from an extremely rich body of knowledge regarding vision) explain why Avicenna (eleventh century) thought that the eye is like a mirror—what is seen is a reflection on a mirror—while Plato (and some of his followers) hypothesized a spotlight view: the eyes put light on the things in the world. Aristotle, in opposition, described a receiving eye. It took some time until dissection would inform more advanced descriptions (of the retina, cornea iris, etc.) based upon which Galen arrived at an analogy with the lens, and to the binocular vision model. Changes in the understanding of what eyes are and in realizing how interactions facilitated by vision take place are amply documented. From early mytho-magical testimony to the Renaissance and up to Descartes (who understood neither vision nor the connection to cognitive processes), visual interaction facilitated by seeing is explained in a sequence that runs the gamut from the intuitive (based on immediate experiences) to the scientific. The lens, ascertained also through the instruments of the time, succeeded as the most accepted description of the "hardware" of seeing; while evolution researchers still wonder why in some organisms the nerves are placed before the lens, and in others, behind. Rich data from a variety of experiments show that the epigenetics of taking the world in through vision is more complicated. What genetic methods usually leave aside–while trying to get to the reductionist end (name the gene of sight, of hearing, of smelling, etc.) or describe how the energy of sensory perception becomes a representation—is the holistic nature of perception. Anticipatory quality is achieved on account of the subtle integration of various stimuli. The senses interact: animals see many things on account of hearing them, smelling them, of touching them, etc. For the human, creating an image of what is anticipated—sometimes right, sometimes wrong—is part of the process. Anticipatory processes are non-deterministic. A deterministic conception, such as genetic reductionism or computational biology, does not make this understanding possible. Epigenetics, properly understood, helps in making clear that living processes are different in nature from mechanical processes.

Sensing, in its most limited sense (no pun intended) emerges as the types of interaction among incipient forms of life and between the and the environment, diversify and increase in intensity. Initially, sensing is probably of the nature of tactility: physical contact. (Regarding the evolutionary origin of sensory processing, see [66]) The notion of syncretism seems to more adequately capture the continuum of the spectrum of living interaction. Millions of years later (the Cambrian mentioned above) extended to smell, sight, hearing, etc. In the examples above the focus on seeing and the eye is meant to suggest the role of the eyes (whenever some are formed) in the change through which incipient life (no eyes as such, rather photosensitivity), of limited sensory abilities, developed. Ongoing research points to the integration of senses: eardrum movements and saccades are in some correlation. They are actually ahead of the eye movement, as a form of anticipatory expression [67]. Even more relevant is the finding [68] that motoric expression and perception are in a continuous state of interaction. Moving affords evolutionary advantage. Rhythms of cognitive activity and rhythms of the external world (environment, in a broad sense) are entrained in each motoric expression. As a result, rudimentary epigenetic processes contribute to anticipatory expression (preparation for a possible future [69]). One might not subscribe to the "mechanics" of experiments intended to document the process. Light emitting diode (LED) flashes are different in their particular physics from natural stimuli. But the inference that environmental stimuli and the sampling patterns of the living organism end up in some correlation (Abassi and Gross [70] report on motor-auditory interaction) is justified.

The importance of seeing brings the eye to the forefront. This prompted many questioning minds to look at what it is, how it functions, how to explain the variety through which we experience it—in essence, WHY? questions. The cognitive leap from the eye considered as lens to the eye identified as a neuronal process, and to a statement such as "We see with our brain" is indicative of alternative views informed by the increased empirical evidence of anticipatory-processes characteristics of seeing. Anticipatory seeing, as documented by Berry et al. [71] in studying the anticipation of moving stimuli by the retina, made it clear that processes related to it are distributed. The research proved that anticipation of moving stimuli begins in the retina.

That genetics describes part of the process is indisputable. It is no longer that we expect the visual cortex to do some heavy extrapolation of trajectory, as in mechanical models that dominated the science of vision (and which continue to flourish since "machines for seeing" are based on it). But we now know that retinal processing, and almost all other vision-related processes are not only in reactions to stimuli, but actually pro-active. Even if pro-activity is not equally distributed along all sensory channels—some are slower in anticipating than others, not the least because sound travels at a slower speed than light does, for example—it defines a characteristic of human perception and sheds new light on motoric activity, itself of anticipatory nature [72].

9 Accounting for Change

Empirical findings concerning vision (for example), or the nature of motoric activity, deserve attention because they document progression from shallow reductionist explanations to deeper and deeper views. The path is from the physicality of the eye (still important to the optometrist, who examines patients for cataracts, glaucoma, macular degeneration, etc.) to its metaphysics. The word is used in its strictest sense: the inquiry into the fundamental nature of reality, the first principles of being, identity and change, space and time, causality, necessity, and possibility. Seeing, or performing an activity, not unlike hearing, smelling, touching, and tasting, are part and parcel of knowing oneself and the world.

To live is to interact with the world. Epigenetics is the knowledge domain that describes the open-ended variety of interactions of genetic consequence. Epigenetic interventions take place within the larger framework of anticipatory processes, which expand beyond epigenetic interventions. They are driven by the survival of life and its creative reproduction.

It is, therefore, necessary to define the nature of what we called interactions.

Axiom 4
To observe the world is to interact with the world.

Corollary 1
To observe is to change the world.

Corollary 2
To observe is to be changed by the world.

Corollary 3
Observations are part of an open-ended cycle of entangled parallel recursions.

How do we account for change? If a witness, i.e., a living entity from another universe that could record change completely disentangled from the world, were possible, it would experience an epistemological conundrum: Being disentangled (sometimes described as objective, unaffected by the observed) ultimately means that the record would be empty. Such a witness, or observer, while conceivable—at least in a description using words, themselves not independent of what they stand for—is rather impossible. In a different context [73], I postulated (paraphrasing [74]) that *One cannot NOT interact.* In a world free of interactions, there is no change to account for, and no need to describe it. All there is is part of the world, and consequently to observe anything in the world is to interact with it. For the sake of simplification, we can separate the changing world (to which the observer belongs) and the observer itself, changing as the world to which it belongs changes. Based upon this simplified model we can consider their interactions (Fig. 9).

Some of these interactions are part and parcel of the dynamics of the world: some random, some regular, some predictable, some unpredictable. Interactions triggered by the actions of observing the world are reflective of the Why? question: Why the succession of day and night? Why warm and cold? Why hard and soft? Why fast and slow? And so on. On top of these particular Why? questions is the WHY? of "Why observe?" Through epigenetic interaction, the lifeless DNA or the genome might become part of the process, but it is not where the answer or answers could be found.

Lifeless matter interactions correspond to the dynamics of change of matter and energy. Living matter interactions are the expression of the self-preservation of life. This is where the immediate answer to the WHY? of "Why observe?" is in plain view: "To maintain life." In other words, in opposition to entropy, resisting decay. The viability domain—between the inception of life and the end—is at the same

Fig. 9 Observing the world and being part of the world

time the domain of the continuous remaking of life. Therefore, epigenetics seems entangled with anticipatory processes driven by the realization of the possible future. At the human level, this is expressed in the postulate "We are what we do." But so is every other living entity, and so are all their constitutive elements, e.g., cells, tissues, organs, etc. You can infer from the whole to each of it, but you cannot infer from the parts to the whole. Reductionism does not cut it! This is even more evident in respect to the DNA—a lifeless crystal, with a unique configuration subject epigenetic action. Inference from the genetic, i.e., chemistry of life, to life processes are always after the fact. All reductionism is by necessity sterile.

10 The Consequential Nature of Foundation Research

The matter-energy interlocking in the living is such that identity is preserved from top to bottom and reinforced from bottom to top. It is not only the individual organism—microbe, yeast, mushroom, worm, spider, cat, elephant, human being—that acts in anticipation—of opportunity, danger, long and short-term changes of all kinds ranging from the day-and-night cycles to catastrophes of all kinds—but each constitutive element. The DNA is fixed: its elaborate double helix structure is meant to preserve it as a whole. The recursive chronicle of successive or simultaneous causal processes experienced via epigenetic interventions, which ultimately change the protein profile of individual organisms, is in itself an expression of observations of self and the medium of existence: *Umwelt*. It is understood as that specific part of the existential reality, i.e., environment, in which everything alive is what it does. Environment integrates the material world—some as living matter, some as non-living matter—and the spiritual. This view is the basis for evaluating the consequential nature of establishing a foundation for a science that integrates the reactive and the anticipatory.

The SAR-Cov-2 virus binds to the receptor human ACE2 (hACE2) through its receptor-binding domain (RBD) and is proteolytically activated by human proteases. In simpler words, a lifeless particle is sucked into the living dynamics of cell activity where copies of the virus are generated. There is reaction to the virus, and there is anticipatory activity. The process documents the anticipatory behavior associated with cell renewal: the self-reproduction guided by the RNA. This example cries for acknowledgment since the entire activity focused on mastering the pandemic focused on an incomplete understanding of epigenetics. Even the spectacular mRNA vaccine, a victory of synthetic biology, reflects this epistemological limitation. Concretely, it is expressed in the worrisome number of breakthrough infections, as well as in the fact that boosters have not diminished the danger of infection (increasing it in some cases). Indeed, to prevent via immune processes, in the sense in which Edward Jenner conceived vaccination, as an anticipatory action, is different from synthetic epigenetic action via the mRNA process. A new booster will not do [75]!

Humans are what they do. The purpose of increasing the number of opportunities transcends the immediateness of preserving life. This often takes place at the expense of other species, i.e., of nature. Some were totally eliminated; others, such as domesticated animals or hybridized plants, were forced into patterns of existence subordinated to those of the human evolving towards a condition of entitlement. As this behavior becomes part of social life, anticipatory action becomes less beneficial. One example: the perils of all kinds of pests related to domestication with the purpose of multiplying food sources (e.g., avian pest, swine flu, mad cow disease, etc.) is the outcome of increased vulnerability.

Lemma 4

To observe the world is an action in anticipation of its change.

To observe the world is more than to record it; it is to make choices in the present for the possible future.

Movement of lifeless matter (e.g., stars, objects, floating pieces of wood, ions in the brain, nucleotides, etc.) is experienced at a level of observation at which answers to the WHY? (Why is it moving?) depends on the scale of perception. As we have seen, Newton's physics and Einstein's relativity theory are such answers. They are formulated in the language of mathematics and were experimentally tested. The formal encompassing description, which Rosen [22] called the largest model, can be formally processed with the same effectiveness with which what the description (usually a mathematical formula) conveys can be manipulated. This gives physics practical significance: marble can be "mined," cut, and processed; Newtonian physics guides almost the entire operation. For that matter, his physics guides the technology of the Industrial Revolution. Descriptions of energy processes guide the emergence of engines.

The same does not hold true for living matter. Observing cycles of a tree (from the germinating seed to a seedling) has no significance for our understanding of its lower-level change. Observing a fish, a lion, a microbe move in the respective universe of their existence is probably a source of knowledge about that particular movement, but not about cell dynamics, neurons, their physiology or even their anatomy—not to mention the genetic process that extends from inception to death (i.e., over the viability domain).

The self-disrupt behavior of octopuses is rather of the nature of their unique biological identity, but not of their chemical make-up—the genetics—or of their physical properties. Change in living matter is of particular interest (and significance) since it conjures anticipation as an integrated expression that does not imply a "largest" model. There is no such thing as the equivalent of gravity or of relativity in the domain of life. Whether quantum descriptions (non-locality, entanglement, superposition, etc.) are meaningful in describing life is still open to debate. However, probabilistic and stochastic understandings, appropriate for describing the non-living, entail the heavy burden of determinism and therefore miss the non-determinism of anticipatory processes. To be consequential, a theory of life must transcend the arbitrariness of right and wrong and focus on the possible. Without future, there is no life.

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