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From the century of the gene to that of the organism

Introduction to new theoretical perspectives

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RÉSUMÉ. *Les organismes, qu'ils soient uni ou multi-cellulaires, sont des agents capables de créer leurs propres normes ; ils articulent continuellement leur capacité à créer de la nouveauté et de la stabilité, c'est-à-dire qu'ils combinent plasticité et robustesse. Ici, nous présentons et articulons brièvement les trois principes proposés récemment pour une théorie des organismes, à savoir : l'état par défaut, prolifération avec variation et motilité, le principe de variation et le principe d'organisation. Ces principes modifient profondément les observables biologiques et leur nature théorique par rapport aux cadres des théories physiques. Ce changement radical ouvre la possibilité d'ancrer la modélisation mathématique à des principes proprement biologiques.*

ABSTRACT. *Organisms, whether uni or multi-cellular, are agents that make their own norms; they continually express their ability to generate novelty and stability, that is to say they combine plasticity and robustness. Here, we briefly present and describe the three main principles that our group proposes for a theory of organisms, namely: the default state, proliferation with variation and motility, the principle of variation and the principle of organization. These principles profoundly modify biological observables and their theoretical nature compared to the situation in physical theories. This radical change opens up the possibility of anchoring mathematical modeling to biological principles.*

1. Introduction [1]

The first decade of this new millennium was nicknamed the post-genomic era. Its arrival was greeted with excessively optimistic statements of both the biological sciences' and the pharmaceutical industry's thought leaders who claimed that new technologies and the reductionist approaches that characterized the second half of the 20th century would cure cancer, lead to personalized and precision medicine and so on. Indeed, the rhetoric and promises have not changed since the time when President Nixon declared the "war against cancer" in 1971, despite the feeble results of this prohibitive enterprise. The last version of this project, proposed by President Obama and aiming to cure cancer "once and for all", faced many criticisms in terms of the cost of the project, the probably minimal impact on prevention and public health politics, the inequalities of access that the cost of personalized therapies would lead to and finally, most notably, the doubtful chance of success [INT 16; BRE 16; BAY 15, JOY 16]. However, we think that it is also crucial to critic the philosophical and theoretical position on which the biological research feeding into this program is based and which has dominated biomedical research for the last 70 years. Moreover, critics must still provide a coherent and operational alternative theoretical framework.

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Although our work in designing a theory of organisms is not based on these sorts of gigantic projects, we consider that the content of our work provides a critical analysis and addresses the limits of the dominant and reductionist view, rich in metaphors and poor in theoretical elaborations. In contrast, in a special issue of *Progress in biophysics and molecular biology* in which AS and GL are the invited editors, we published the different results from our research group touching on the elaboration of a theory of organisms. This issue analyzes the role of scientific theories not only for their epistemological function of permitting intelligibility, but also as practical tools for framing research and the construction of objectivity in experimental and mathematical models. More importantly still, the articles it contains highlight main fundamental principles that contribute to designing a general theory of organisms.

Since Aristotle, the concept of a strain towards an aim, or teleology, was used to understand one of the main characteristics of organisms, the "aim" of staying alive. An example of this is demonstrated by the goat studied by [SLI 42a, SLI 42b]. This animal was born with paralyzed front legs and quickly learnt to move around by jumping on its back legs. This behavioral adjustment led to major morphological changes in the bones of the back legs and the pelvis as well as in the pelvic muscles [WES 05]. Two millennia after Aristotle, another great philosopher, E. Kant, worked on the difference between knowledge of the inert and of the living. In terms of teleological thinking, he showcased the links between the organism and its parts and the circular causality implicated by these relations. He describes teleological judgement as an organizer principle enabling the understanding of a biological object across its unity (this object being the cause and effect of itself), before individually describing its parts. After Kant, teleology was adopted as heuristic by teleomechanics [LEN 82]; for Blumenbach, the *Bildungstrieb* (life force) was a teleological agent whose cause, much like that of Newtonian gravity, was beyond the reach of Reason. However, the consequence of this organizer principle, as with gravity, is that it can be subject to scientific analysis [LEN 80]. Thus, teleology was a particularly useful concept for the development of several biological disciplines at the end of the 18th and 19th centuries.

Several historians, philosophers and biologists have described the overall changes in the practice and conceptualization of biological phenomena that occurred in the 20th century [MAY 96; GIL 00]. One of them, Lenny Moss, describes "the phylogenetic turn" as having changed the perception of the organism. He thus stated: "the theater of adaptation changed from that of individual life histories, that is, ontogenies, to that of populations over multiple generations, that is, phylogenies.". Moss's phylogenetic turn imposes a choice "[…] between a theory of life which locates the agency for the acquisition of adapted form in ontogeny—that is, in some theory of epigenesis versus a view that expels all manner of adaptive agency from within the organism and relocates it in an external force—or as Daniel Dennett [DEN 95] prefers to say, an algorithm called "natural selection" [MOS 03]. Due to this change, agency, normativity and individuation, until then considered as the main characteristics of life, nearly disappeared from the biological language. Since then, cells and organisms have become passive beneficiaries of a program. Consequently, it is not surprising that modern biology is equipped with a theory of evolution, but not a theory of organisms.

Despite the strong influence of teleomechanics, their point of view has not been universally accepted; in fact, two contradictory streams have emerged in biological thinking. Their main difference lies in the hypothesis that there are singularities in the living that require a different perspective from that used in mechanics. The long debate between these two positions continued into the 20th century as a polarization between reductionists and organicists, even though the former had moved from the view of a mechanical world to the view inspired by mathematical and computational theories of information [LON 12]. Effectively, the introduction of the notion of a "program" [PER 16, LON 12] was seen as a theoretical means to dispense with the concept of teleology [MAY 96]. However, the adoption of metaphors and powerful tools designed and used by reductionists blurs the distance between these two streams (see [PER 16, LON 12]). The current state of affairs is such that even biologists who consider themselves organicists very often use the omnipresent language of molecular biology, a language that confers causal power to molecules, and particularly to genes. Nowadays, the main difference between reductionists and organicists is that the latter are very conscious that, when they.practice reductionist analysis, they run the risk of destroying the very phenomena that they aim to understand. The search of observables specific to biology has been ongoing for centuries. The 18th century naturalists had a real passion for describing of the observable characters of beings; theirobservations, in fact, made possible the analysis of species and their historical dynamics through Darwin's theory of evolution.

The choice of pertinent observables is at the heart of all theoretical design [LON 16]. In Physics, very different theoretical frameworks have been proposed on the basis of "simple" changes in scale: quantum,

hydrodynamic, relativist; it suffices to change scale and new observables are identified and analyzed through conceptually and mathematically different, often even incompatible, theories [CHI 15].

In the second half of the 20th century, the sensational arrival of a new object of knowledge, ie, information and the theories about its transmission and elaboration, provided new possibilities for scientific invention. Nowadays, an invisible flow, moving at the speed of electrons or photons, organizes the world independently from its material realization. Indeed, the software is independent from the material from which the hardware is made. Ever since Turing' discrete state machine, and Shannon's work on transmission of information, signals have been elaborated, and transmitted (Shannon), as discrete sequences of signs. From this perspective, could "an aperiodic crystal", such as DNA, have the function of coding for heredity? Schrödinger's famous 1944 conjecture was notably original and even audacious when first proposed: it suggested that in one dimension, it was possible to code for three-dimensional structures. The existing codes, invented by Morse or even Gödel or Turing in the 1930s, had coded sequences of signs with other signs, or with numbers, nothing more. Probably no one had yet envisaged using this strong property of discrete mathematics: *discrete* mathematical manifolds in any finite dimensions can be coded in a single dimension, with no loss of the relevant mathematical invariant properties. Furthermore, Schrödinger understood the implications and limitations of his conjecture: he observed that, if true, the organism must be viewed as a Laplacian machine in which determination guarantees predictability (p. 7). Turing acknowledged the Laplacian nature of his own machines. When Monod stated that "the cell is a Cartesian machine", regulated by "a Boolean algebra, as in computers" [MON 70] he was perfectly aware of the Laplacian structure of determination it imposed on biological objects: computers are determinist and predictable, despite a few possible random events (noise) in concrete computers, although very rare and controlled [LON 10]. This is how the mathematical concepts of information were transferred to biology. A consequence of this transfer was the attribution of biological information to molecules. The latter, seen as discrete structures, construed as the atoms of the living, become the location of ultimate reduction of all forms of biological knowledge. Indeed, a type of knowledge which is grounded on a radical determinism [LON 15]. The exact stereospecific of molecular interactions will guarantee the transmission and elaboration of information, exactly, like in a computer: "evolution is due to noise" [MON 70]. Information is therefore a logical flow, independent from the hardware, or the materiality of the biological, whose physical body simply becomes the vehicle for genetic information [GOU 02]. Digital information is thus independent both from the hardware and, as mentioned above, from the dimensions of the space of the dynamics. In digital machines this is a key property which allows defining "Turing's universal machines" as well as today's operating systems and compilers, encoded by digits in the same dimension as programs and data[2]. That is, the beautiful invariance properties of information theoretic approaches (independence from the hardware and from dimensions) imply major properties of computing and signaling. Moreover, to become a functional ontogenetic program, genetic "Boolean algebra" requires this unidimensional universe in which biological bodies and their physical interactions, such as those present in morphogenesis for example, have no place. By contrast, physical properties of geometric nature, such as any dynamics of forms, are strictly dimensional.

In addition to the conceptual problems generated by the "phylogenetic turn", the information-based revolution of molecular biology, dematerialization and a-dimensionality in particular, led to the prominence of digital information and the accumulation and exploitation of huge databases. Together with the lack of an encompassing "theory of organisms", the abundance of data has led to the notion that the scientific method is obsolete [AND 08]. Analyses of molecular Big Data (transcriptomes for example) should dispense with all attempt to understand and theorize. Instead, it was proposed that the analysis of correlations would be sufficient to predict therapeutic outcomes. However, it must be noted that, in spite of the claims of the proponents of big data science, this approach is neither hypothesis free nor free of ideological bias. On the contrary, these analyses are epistemologically subordinate to a theoretic outlook, for the most part a tacit one, and particularly by the choice of what is observed, the choice of the metrics and the priorities given to different data – usually of a multidimensional nature. Moreover, transcriptomics, regardless of the size of the database, is blind to the distribution of mechanical forces, so important in morphogenesis, or electrical fields, crucial for the heart and the nervous system (see also [CAL 16] for a mathematical critique of these theses).

An additional consequence of the information and computational approach made "necessary", in the word used by Monod recalled above, the assumption of exact stereospecific and chemical interaction of macromolecules, in particular under the form of the "key-lock" paradigm for the "hormonal signal" and cellular

[2] A consistent search for operating systems, compilers and even Gödelian effects in the DNA as a formal system for computations, may be found in [DAN 03], [DAN 08]. See [LON 18] for a closer analysis.

receptor. This is the most reasonable assumption to be made if one wants to elaborate and transmit information in and by macromolecules. However, experimental evidence shows that biological specificity cannot be reduced to stereospecificity [SOT 05]. Also the "central dogma" of molecular biology (the unidirectional transmission of information from DNA to RNA and then to proteins) is a necessary assumption under the hypothesis of the informational and "instructive" role of the DNA in ontogenesis. Both these fundamental assumptions introduced by the molecular biology revolution are increasingly acknowledged to be wrong (a broad literature may be consulted for this, recent advances are in [MAR 14]). Thus, the Laplacian properties of stability and invariance proper to the two major theories of information on discrete data, were implicitly forced into the biological context without a proper critical analysis of their pertinence. This ideology resulted in the reification of the mathematical concepts of program, information and signal, which still guide the choice of biological models and the design of experiments. Unfortunately, the use of the fashionable concepts borrowed from the computers' world has been very effective on the non-scientific readers, including bureaucrats and politicians deciding research financing. In order to describe the phenomenon, we may transpose the effective wording used by [SOK 97] concerning some contemporary philosophers: those that use information theory and computational concepts in molecular biology … "have repeatedly abused scientific concepts and terminology: either using scientific ideas totally out of context, without giving the slightest justification— note that we are not against extrapolating concepts from one field to another, but only against extrapolations made without a argument— or throwing around scientific jargon in front of their non-scientist readers without any regard for its relevance or even its meaning. We make no claim that this invalidates the rest of their work, on which we suspend judgment". This is more closely argued in [LON 12], [PER 16], [LON 18].

By following other paths, the proposed perspective throughout this article and the issue mentioned above returns to underline the radical materiality of the biological, including spatial dimensions of organism, and to return to the scientific method rather than to oppose it. Thus the objective of our work is to propose theoretical principles for the construction of a theory of organisms that can overcome the obstacles arising from the reductionist viewpoint and/or based on the notion of information generated from the 20th century, and avoiding the choice imposed by the Modern Synthesis between phylogenetics and the organicist approach.

We then work in a different direction and begin, following Darwin, with the choice of *organisms* as pertinent observables. We also start with the cell, for which we propose an explicit hypothesis. We suggest principles that seem robust to us, put forward following observation and experiments.

Based on the organicist tradition, we propose three principles to elaborate a theory of organisms: 1) the default state of cells as proliferation with variation and motility, according to cell theory [SOT 16], 2) the principle of organization, following Kant's lines and a recent approach to theoretical biology [MOS 16], and 3) the principle of variation [MON 16a], in continuity with Darwin's work. We have recently provided examples of the way in which these principles can guide biological research on morphogenesis [MON 16b] and cancer [SON 16].

2. Philosophical positions

Contrary to evolutionary biology, organismal biology, as we observed, does not yet have a largely accepted overarching theory. For this reason, it would be very useful for the practitioners to explicitly state the principles, postulates and concepts that underlie their research; in short, their philosophical positions. From the organicist view developed here, biological objects are characterized by the simultaneous coexistence of opposites as shown by their variation and stability, the incomplete separation between interior and exterior (topology) and between before and after (time). The latter leads to notions of an extended present, of memory and anticipation [LON 11b; MIQ 16]. From a thermodynamics point of view, organisms are open systems that canalize flows of matter and energy which enables them to maintain their metabolism. The internal constraints of such an object are always affected by external constraints; thus, in order to understand what is happening inside the system, the multiple levels in which this system is integrated must be accessed at the same time [STE 97]. For example, the cell in its entirety is integrated in a more complex system, the tissue, the organism, in which it does not have the same behavior as seen when placed in a conventional *in vitro* culture. For example, in a cardiomyocyte, proteins that channel ions (calcium, potassium) transport charges that modify the voltage of the cell. In response, the voltage within the cell changes the ionic channels [NOB 06]. Thus, these elements modify the behavior of the heart and the heart modifies the behavior of its components and both the components and the heart are integrated in a higher multicellular structure, the organism. This means that the functioning of such a system is

never only defined by its initial conditions. The biological object is historical and undergoes constant changes, from fertilization to death. The biological object is always in construction and remodeled through the course of its life.

In summary, the way in which an organism constitutes its historical trajectory is not a consequence of its initial description. Instead, it works to produce something new (qualitative and structural) in the real world [MON 16a]. Thus, emergence, understood here as the appearance of new observables through time, is not a simple epistemic property. It has ontological and theoretical significance [SOT 08].

3. From inert to living

Physical theories are founded on stable mathematical structures, based on regularities and especially on theoretical symmetries. In the theories of physics, objects are both defined and understood thanks to invariants and invariant preserving transformations. These operations allow understanding changes as changes of position in abstract spaces, that is, changes of state. Such a space is objectified as the space permitting the theoretical determination of objects by equations and ultimately specifying their trajectories (generally effectuated by optimization principles). This method ultimately corresponds to the study of generic objects, namely, the collective study of a variety of situations and concrete objects as theoretically equivalent. In summary, physical objects are generic and their trajectories are specific [LON 16, MON 16a].

By contrast, biological variations are strong, frequent and qualitative enough to justify that biological objects cannot be considered as generic. We assume the contingency of biologically relevant mathematical structures and in particular of theoretical symmetries. Biological changes include change of symmetry and equations with the passage of time, such as when a zygote develops in an adult animal or in evolution. Biological objects, organisms, are specific and, in consequence, they are not interchangeable. Their trajectories are generic; they are not specified by the space of description [LON 14]. These biological objects are the result of a history representing a cascade of changes in their symmetries and a continual "re-use" of existing phenotypes and genotypes, a process which depends on rare events [LON 17]. They demonstrate variability, contextuality and historicity [MON 16]. In addition, organisms are not only capable of creating their own rules, they are also able to change them [MIQ 16, CAN 91, MOS 16, MON 16, SOT 16]. This point constitutes our principle of variation [MON 16].

4. Cell theory: a starting point towards a theory of organisms

Canguilhem traces the history of cell theory back to the 18th century and distinguishes two main aspects, each addressing a fundamental question, namely i) the composition of organisms, with the cell as the element "carrying all the characteristics of life", and ii) the genesis of organisms. Canguilhelm attributes the idea of linking these two components to Virchow [CAN 08]. The second element of the theory, the genesis of organisms, is, of course, applicable to both unicellular and multicellular organisms. In addition, since the formulation of cell theory, the egg in which multicellular organisms develop is considered to be a cell whose behavior can be explained as the division of the aforementioned cell into daughter cells through cell proliferation. In this regard, the cell was, according the Claude Bernard, a "vital atom": "in all deep analysis of a physiological phenomenon, we always reach the same point, the same irreducible elementary agent, the organized element, the cell" (Claude Bernard Scientific Review, September 26th 1874 – quoted by [CAN 08]). From this dominant position at the end of the 19th century, the theory has maintained itself and survived the question of whether syncytia are compatible with the cell structure of multicellular organisms, from both an anatomical and functional perspective. Another problem debated since the works of Virchow touches on the individual status of cells. In the case of unicellular organisms, there is no issue stating that the cell and the organism are one and that they are therefore individuals. However, attributing individuality to cells in multicellular organisms, as well as to the organism that contains them, created problems that led some people to reject cell theory. In our view, it is the concept of the entanglement of levels that provides a useful perspective on the relationship between the organism and the cells: the zygote is both a cell and an organism, and with each cell division through the course of development, these two levels of individuation become more evident. In other words, we can adopt the Simondonian philosophy and regard individuation as a process rather than seeing the individual as a thing [MIQ 16].

At the time of its formulation and still today, cell theory plays a federating role between evolution biology and organism biology; it provided a link between the individual and its descendants in which the cell itself is a vehicle of heredity.

5. The founding principles: from entanglement to integration ?

5.1. *Genealogy of the three proposed principles : the default state, the principle of organization and the principle of variation*

Each principle has its own history from before the creation of the "organism" group. The default state was initially proposed by Soto and Sonnenschein [SOT 91] and was based on experimental work carried in the early 1970s to study the role of estrogens in the proliferation of their target cells. This principle is founded on cell theory and the strict materiality of life. The default state is anchored in the idea that the cell is an organism and is the origin of all organisms. The joint work of Longo, Montévil, Sonnenschein and Soto resulted in the integration of variation in the default state of proliferation and motility: each cell division generates variation [LON 15]. The works of Miquel, Soto and Sonnenschein also addressed the generation of new observables whilst also examining the concept of emergence, descendent causality and the entanglement of levels [SOT 08].

The principle of variation can be attributed to Bailly, Longo and Montévil's analysis of the differences between physical objects and biological objects, the notion of extended criticality [LON 11a, LON 16], certain works by Kauffman [KAU 02] and, of course, the Darwinian idea of descent with modification[3]. The principle of variation affirms that an organism is always the possible object of qualitative changes, potentially unpredictable and pertinent, for its functioning. These constant changes described by the principle of variation highlight a major difference between the theories of the inert and those of the living, discussed in section 3. The other side of the coin, namely stability, must therefore be addressed through its own principle as there is no equivalent of axiomatic validity within the fundamental hypotheses of physics (the laws in their mathematical form) and the principle that fills this role for us is the principle of organization.

The principle of organization comes from previous work in theoretical biology, such as the notions of autopoiesis [VAT 74], of closure [ROS 91] and work-constraint cycles [KAU 02], that have been reinterpreted by Montévil and Mossio as closure of constraints [MON 15, MOS 16]. The principle of organization stipulates that the biological systems implement this closure, which is to say that the pertinent biological constraints (of the organism) are interdependent. In our context, the principle of organization is a fundamental source of biological stability. The notion of closure between constraints is a means of reaching and maintaining a relative organizational stability, in change, and has traditionally been applied to intracellular processes. Mossio et al consider the concept of constraints as conserved through the time of the constrained process [MOS 16]; this concept opens an entry point for the theoretical founding of mathematization of organisms without losing sight of the organism itself. We have used this notion to model the morphogenesis of mammary glands, from the default state of cells and the constraints that are applied to it [MON 16].

5.2. *How to organize these principles into a coherent ensemble?*

Our theoretical work addresses both unicellular and multicellular organisms. In analogy with Darwin's strategy regarding phylogenesis, it seems prudent to put aside the transition from the prebiotic to the biotic world, and we propose rooting our principles in the biotic world. In so doing, we understand that we are agnostic in terms of knowing whether the principles we put forward for the study of organisms are pertinent to the abiotic world, since even a hypothetical biochemical structure capable of instantiating closure is not an organism, and a molecule able to self-replicate is not an organism capable of multiplication (e.g. prions). Actually, if a cell could be obtained built from chemical compounds, it would differ from current biological cells

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[3] The concept of extended criticality comes from the physics of "critical phase transitions", the processing of the emergence of a new object, such as the transition from water vapour to snowflakes. A phase transition occurs at a certain point, the "critical temperature". This point marks the passage from one symmetry to another, and from one macroscopic object or one structure to another. Extended critical transitions, on the other hand, concern a non-trivial interval such as the lifespan of an organism. In this context, an organism continually undergoes critical transitions in which both objects and symmetries change. The organism and its components are reconstructed permanently but with variations.

because of its lack of historical past. We should distinguish the time of (physical) processes from historical time, which is truly biological [LON 17].

The three principles that we propose are irreducible one from the other and none can be interpreted as a possible condition of the other two, at least in this first analysis regarding their articulation.

5.2.1. *The role of the default state*

The biological default state (proliferation with variation and motility), expresses biological agency and makes a causal structure explicit. Our proposition for the default state has immediate consequences on that which requires an explanation in terms of theoretical cause. The default state does not necessitate such a cause. On the contrary, what requires explaining is a departure from the default state (quiescence, restricted variation, lack of mobility, see [SOT 16]). This notion of theoretical cause must be distinguished from the notion of differential cause, which means that a difference introduced into a system, such as a carcinogenic product, leads to a difference in the behavior of the system. In order to move from a differential cause to a theoretical cause, it is necessary to understand how the differential cause modifies the constraints acting on the system [LON 16]. In addition to physical constraints, there are also chemical constraints that affect morphogenesis. For example, those imposed by collagen, phospholipids or DNA. The ability of an organism to generate new constraints produces diversity.

5.2.2. *The role of constraints*

Biological constraints and their actions are a key objects of biological research in the context of a theory of organisms. All the suggested principles in this issue are tightly linked to the notion of constraint, and conversely, this notion is shaped by the founding principles put forward.

The default state is rooted in cell theory and the notion of the cell as an agent. Constraints are much simpler objects than cells, and understanding the action of constraints on cells requires a specific principle: the constraints work by moving cells away from the default state. Placing a default state on cells allows us to discuss the action of constraints on the cells, which is to reduce, impede or channel their ability to proliferate and move. This approach overcomes the metaphorical and anthropocentric utilization of the notion of a signal while still recognizing the agency of cells. Cells are no longer passive things, like stones, on which we must act in order for them to do something (proliferate or move) [SOT 16].

The principle of organization leads to underlining the role of constraints in terms of the unity of organisms, and thus to evaluating whether a given constraint is functional, whether it participates in closure. The constraints of an organism are constraints that are both maintained by other constraints and in turn maintain other constraints. Bearing in mind the interdependence of the organism and its parts, it is never enough to analyze a given constraint or a set of given constraints in isolation. Constraints have to be analyzed in the context of the organism, even though more local analyses can be relevant. For example, an analysis of constraints on the default state helps to understand glandular morphogenesis in a 3D model of the mammary gland, at the tissue level [MON 16]. As mentioned in this article, supplementary constraints at the tissue level and the regulation by the organism, via hormones, are obvious and necessary additions for a more complete biological analysis. In summary, supplementary constraints must be taken into consideration to understand the overall biological organization in which the studied phenomenon, morphogenesis in mammary glands in this case, is rooted.

The principle of variation is instantiated in the default state, given that each cell division generates two similar, but slightly different cells. The principle of variation is also applicable to supra-cellular levels in the Darwinian notion of progeny with modifications as seen in morphogenesis. The principle of variation states that constraints are not necessarily phylogenetic or even ontogenetic invariants. In contrast, constraints are subject to variations. For example, a morphogenetic process described in biophysics as a set of constraints is not necessarily conserved in the lineage. Instead, it is generally modified as much for specific individuals as for groups of individuals, for example in a specific layer. Constraint changes are therefore intrinsic in the notion of biological constraints.

6. Conclusions

Scientific theories propose organizing principles and construct objectivity by framing models, observations and experiments. Many mathematical concepts and structures come from the analysis of physical phenomena; these mathematical innovations, in turn, have helped to arrange physical concepts in new, more meaningful ways. A classic example is the invention of Newton's infinitesimal calculus, inspired by the analysis of the body's movements, leading to notions of speed and acceleration. The infinitesimal calculus makes these mathematical concepts intelligible and the movement of planets thus acquired a new mathematical objectivity. Riemann's geometry, inspired by the geometrical analysis of Newton's gravity, was invented in the 19th century and later used by Einstein for Relativity in the 20th century. Dirac's delta, Feynman's integral and totally new theories such as Weyl's gauge theory were entirely inspired by quantum and relativistic physics. As in the previous examples, these mathematical inventions bring a new light on physical phenomena. They are simply examples of a creative synergy between disciplines. Why is this not the case in biology?

Symmetries and conservation laws are intricate notions that play as fundamental a role in mathematics as in physics; they are tightly bound to the common genericity of objects, mathematical or physical, and to the specificity (unicity and mathematical optimality) of physical trajectories. On the other hand, variation is at the heart of the theory of evolution and the theory of organisms that we have sketched and intend to develop; it correlates with the specificity (historicity, individuation) of the biological object, as well as with the genericity of evolutionary trajectories [LON 14]. We hypothesize that the consequences of the variation principle, and the conceptual complexity that is associated with its interaction with stability, explain why biology still hasn't inspired mathematicians to create structures that could open up the possibility of formalizing biological concepts, as was often the case with physics. However, underlining the differences between inert and living objects opens the way to a better understanding of what is needed to reach a possible objective: the development of a mathematical biology playing a similar role to what mathematics played in physics, and distinct from applied mathematics coming from physics that remain frequently used to model biological phenomena [LON 15].

Biological objects are agents able of creating their own norms; they constantly harmonize their ability to create novelty and stability. Postulating the three principles described above also opens the way to a better understanding of morphogenesis and carcinogenesis [MON 16, SON 16]. These principles profoundly change both biological observables and their determination in terms of the theoretical contexts of physical theories. This radical change opens up the possibility of anchoring mathematical modeling on strictly biological principles. Turing showed that there is an epistemological gap between imitation and modeling [TUR 50, TUR 52], as highlighted in [LON 08]. Whereas the second is based on a theory regarding a modeled object and takes into account its causal structure, the first is not – Turing's famous "imitation game" aims at misleading an investigator. Thus, biological principles are necessary to go beyond imitation, seen as the reconstruction of a phenomenological similarity. For example, our model of morphogenesis of mammary ducts is based on the default state and the constraints generated by epithelial cells [MON 16b], that is the modeling is based on principles that propose a potentially causal understanding of phenomena *By identifying the constraints on the default state, multi-level biomechanical explanations become as legitimate as those at the molecular level.* Finally, analysis of the differences between the physics of inanimate and living matter leads to the proposal of three principles that provide a viable perspective for the construction of a necessary theory of organisms. In addition to this theoretical components, these founding principles have been used to frame experiments and mathematical modeling.

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