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On the Status of Biology: On the Definition of Life

Stating that biology is the "study of living things", or processes that take place in the latter, comfortably sidelines what is meant by the "life" part of this term, which is supposedly their *sui generis* characteristic in comparison to "non-living things". Without doubt we can make the observation that the definition of life can only be an ideal point of view, otherwise seen by some as useless speculation. However, insistence on the question demonstrates the originality of biology in comparison to other disciplines that do not appear to have this type of requirement. Physics, for example, does not need to "define" matter or energy in order to study the phenomena in which they intervene, giving them instead the role of "variables" that can be manipulated, whether theoretically or experimentally. Let us recall the basics of the fundamental concept of force, introduced in Newton's second law, using which we can deduce a satisfactory definition of it by multiplying the mass and the acceleration of a movement[1].

Let us return to C. Bernard, who provides an explanation of the notion of life. Stating that "physiology is an experimental science [that] has no place giving a priori definitions", he considered that "it is illusory and irrational, contrary to the very spirit of science which is to seek an absolute definition"[2]. In fact, we can state that biology ignores the notion of life, whereas this is paradoxically the purpose of its field of study. In summary, he goes as far as saying that the field refers to objects that common sense describes as "living". But this does not prevent the definition of

1 Nevertheless, let us note that Poincaré considered the criss-crossing, the vicious circle, to be inextricable and to consist of defining the mass by the force or *vice-versa*. Poincaré, H. (1968). *La Science et l'Hypothèse*. Flammarion, Paris, 118.
2 Bernard, C. (1885). *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux*, vol. 1. Librairie J.-B. Baillère et fils, Paris.

"living things" (as opposed to "life" itself) – moreover, we prefer to talk about singularity rather than look for a true definition of it – remaining a theme of reflection, the subject of university PhDs, stimulated by the latest developments in research on the initial conditions of appearance of life, as well as sometimes by metaphysical considerations that we do not need to include here.

Unfortunately, this pragmatism can only sideline, without resolving, the remaining reason for the existence of the debate. There is, in fact, a debate to be had if we note the diversity of the points of view, ranging, for example, from the statement by the biochemist Szent-Györgyi that "life as such does not exist", to attempts at a definition, if not about the word "life" designating a specified entity, then at least about the nature of what makes an organism "living". Although Aristotle proposed a fundamental definition of it, based on a property of autonomy and self-reproduction (see Chapter 3), modern biology considers that life is an abstract entity that it is unable to characterize. François Jacob expresses this in the following way:

> "Life is a process, an organization of matter. […] We can therefore study the process or the organization, but not the abstract idea of life. We can attempt to describe and we can attempt to define what a living and a non-living organism is. But there is no 'living matter'"[3].

Let us agree that the designation "living matter", refused in the above, is simply a convenience of language, like the famous "vital force" advocated by vitalists. And, since it is necessary to take a side, let us admit the following position concerning our subject, which will be illustrated several times over in the following.

DEFINITION.– Any living object is a precise assembly of interactive "elements" (meaning matter, energy, information), and a system of this kind always faces a risk of instability. It is therefore necessary to search for the structural characteristics and dynamic properties that ensure correct maintenance, development and reproduction of it.

Faced with this issue, mathematics, which is itself a science of structures and transformations, steps up to participate in this study and, better still, to establish a coherence of dynamic representation, in part invariant and in part fluctuating (adaptation).

With this in mind, we can refer to the principle stated by H. Atlan (and independent of its position with regard to the deterministic/random debate): "The only specificity of living things relates to the complexity of their organization and

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3 Jacob, F. (2000). *Qu'est-ce que la vie ?* Éditions Odile Jacob, Paris.

the activities that accompany them”[4]. Obviously, we need to specify this notion of complexity and distinguish it from what it is in non-living systems (Chapter 3). In the meantime, let us say that the notion of life, understood in this way, consists of admitting the following property.

PROPERTY.– The most characteristic processes of any living thing, which can be described as *sui generis*, are *autopoiesis* (continuity of an autonomous production of oneself) and *compliant reproduction* from one generation to the next.

Without spending too much time on this question, we at least need to agree on what and how biology presents a demonstrated specificity with respect to other disciplines, leading us to say, in the words of the biologist E. Mayr, that it is “a science unlike any other”[5]. We call on some past considerations in order to do this.

Let us first recall that the word “biology” is relatively belated, dating back only to 1802, proposed jointly by J.-B. de Lamarck in France and G.R. Treviranus in Germany. For G.R. Treviranus, “biology or philosophy of living nature” (“Biologie oder Philosophie der lebenden Natur”) must aim to study “various phenomena and forms of life, the conditions and laws that dictate its existence and the causes that determine its activity”[6]. For his part, J.-B de Lamarck entitled one of his lessons “Biology or considerations on nature, faculties, developments and the origin of living bodies” (1812). Moreover, he specified:

> “The name of living bodies has been given to these singular and truly admirable bodies… They effectively offer, in themselves and in the various phenomena that they present, the materials of a particular science that has not yet been founded […] and that I shall name biology”[7].

With this new terminology, the objective appears first as the desire to group together all the studies, scattered to a greater or lesser extent, that relate to living things, going beyond the observation and classification of living things whose morphology was the basis for recognition, naming and classification. This first requirement did not prevent a reasoned practice of the use of living things developing in parallel within this natural history, duly distinguished by their nature and their state of development (pharmacopeia, feeding, clothing, housing). This implied a technical experimentation that should not at all be considered negligible

4 Refer to Stewart, J. (2008). La Vie existe-t-elle ? Déterminismes et complexités: du physique à l’éthique. In *Colloque Cerisy*. La Découverte, Paris, 145–158.
5 Mayr, E. (2004). *What Makes Biology Unique?*. Cambridge University Press, Cambridge.
6 Quoted in *Encyclopedia Universalis*.
7 *Ibid*.

(harvesting and hunting, then agriculture and domestication). But the most important point in this "profession of faith", namely biology, is now to consider life as a singular phenomenon whose two aspects are specified by it as: its generality and its diversity. A two-fold task is therefore assigned to this new discipline: (i) looking for properties or characteristic laws that have a certain universal value and (ii) studying the diversity of how these are manifested in reality, including the truly historical aspects[8].

The eruption of the word "biology" is often (wrongly) considered as the declaration of the status of this discipline as a true experimental science. At least, this was written by F. Magendie (1783–1855), in reference to Galileo, writing in his era in his *Principe élémentaire de physiologie* [An Elementary Treatise on Human Physiology] (1833): "in order to know nature […] it was necessary to observe and above all interrogate it via experiments". This position was taken up and developed by C. Bernard, who studied the lessons given by Magendie, and whose successor he became at the Collège de France.

In fact, it must not be forgotten that experimentation on living things has been around for a long time. Let us recall a few notable examples. In Antiquity, we have Hippocrates and his experimental studies on the development of a hen's egg. Then the 17th Century provides us with remarkable research by W. Harper (1578–1657) on blood circulation. An important point is that the originality of these studies was the methodical implementation of quantitative measures of blood flow under different conditions (application of a tourniquet, then its release). Let us note also in this era the tests by L. Spallanzani (1729–1799) that led to the disproving of the theory of spontaneous generation and the highlighting of the role of gastric juices in digestion.

Natural history therefore realised very early on that the anatomical description of structures must precede research into their functioning, without remaining limited to questions of compared morphology and classification, which led to progressive labeling of the reality of various fields of study of phenomena involving living things.

1.1. Causality in biology

On the sidelines of this fundamental topic, it is necessary to mention an old question that has been around in the field of biology for a long time, in

8 On this point, interested readers should refer to Gayon, J. (2004). De la biologie comme science historique. *Sens public* [Online]. Available at: https://www.sens-public.org/IMG/pdf/SensPublic_Jean_Gayon_Biologie.pdf.

particular in embryology, in reference to whether the development of an organism consists of deployment of pre-existing structures in the egg, or, on the contrary, whether ontogenesis takes place according to a spatially and temporally organized sequence of generating processes. This was the famous dilemma of "preformation versus epigenesis". We all have in mind certain famous figures from the past in anthropology, illustrated representations of a miniature being (*homunculus*) that is thought to be housed either in the head of the spermatozoid, or in the ovum. This debate was already alive in the era of Aristotle, who was a supporter of epigenesis or the progressive formation of a series of structures. For a long period of time, this position remained up to date, fed by various staunch positions in which naturalists and philosophers played a part, as well as physicians such as Maupertuis who, supporting his ideas with interbreeding and cross-breeding, was firmly opposed to any idea of preformation. The issue is significant because attributing a causal nature to the notion of preformation is the same as being opposed, automatically, to both reproduction and evolution.

Although the debate eased off with the advent of cellular theory at the end of the 17th Century, which designated the cell as the elementary level where we can site both reproductive activity (mitosis) and various morphogenetic and physiological processes, the theory of preformation is still present in biology. It is of course a renewed form, but one that should be mentioned in relation to the general principle of causality. A first aspect of this persistence can currently be seen in the significance that it is often necessary to apply to the initial conditions of a morphogenetic process. In fact, this consists of taking into account the initial state of a cell at the time of its formation, as a material cause (in Aristotle's sense) of a process. Although this idea of predetermination should be distinguished from the deployment of a pre-existing structure, the initial state is indeed equivalent to a pre-requisite driving factor that participates (in part) in the advancement of a process. Thus, any change in the initial state can modify, both qualitatively and quantitatively, the dynamic of the aforementioned process. Another aspect, amongst the most remarkable, was provided to us by genetics as soon as this broke free from its initial principle of direct, linear and unidirectional causality, from gene to function. The discovery of development genes (with the existence of homeobox genes) in fact underlines this fundamental property of the genome that is to possess a complex topological and temporal structure, non-linear in its organization and its operation. It follows that the ontogenesis of an organism needs to be related to this "preformed structure" whose temporal evolution takes on the meaning of a multidimensional "deployment", not of the genome itself as a physical object, but more exactly of the information that is written in it. Which can be translated by saying that the "homunculus is indeed represented on chromosomes"[9].

To organize the subject, we first need to sum up the position of the principle of causality, the basis for all scientific knowledge. Although it is used very frequently, the debate continues around what is meant by "causality". Let us sum up by saying that, in a more general manner, the function of this term can be given as follows: "reconstituting links, adding events that at first glance are disjointed into a timeframe"[10]. It is a search for an ordered sequence of elements that are linked not necessarily by immediate proximity (spatial or chronological), but by the non-circumstantial fact that they find themselves together and in a given orientation on a single arrow of time, one which allows a given process to be structured. This is illustrated by representation on a directed graph, connecting two elements of the same set, covering the immediate direct effects just as much as the delayed effects (such as an incubation period or a dormancy period) or retroactions (feedback).

This point of view, distinguishing causality and correlation, conveys an ontological character to the idea of causality: the succession of phenomena over time necessarily determines what happens during the evolution of a being or of a system[11]. Remaining on this theme, the question arises of whether there is a link between the proven existence of causality and the explanatory nature of our concepts and models. Some advocate that there is, believing that a mathematical model works (in the sense of simulation) because it explains even a little of the information that participates in causality. Now this needs to be explained further, because if a model is capable of bringing characteristic properties, the latter can come from a simple statistical correlation or from a causality. Moreover, we will see that in terms of modeling, we can be brought to make a mathematical distinction between a deterministic part and a random part, respectively corresponding to what we study in terms of inventoried causes and what we do not know about in terms of unknown or inaccessible causes.

We are aware of how much the natural sciences, including biology, were influenced for a long time by the thoughts of R. Descartes, who stated that it is necessary to move "from what is most simple to what is most complex in the order of deduction" on the basis of "these long chains of very simple and easy reasons that geometricians make use of in their proofs"[12]. The principle of these "chains of

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9 Prochiantz, A. (1994). *Forme et Croissance*. Le Seuil, Paris, 19. French translation of Thompson, D'A. (1992). *On Growth and Form*. Cambridge University Press, Cambridge.

10 Andler, D., Fagot-Largeault, A., Saint-Sernin, B. (2002). *Philosophie des sciences*, vol. 2. Gallimard, Paris, 825.

11 Refer to Kant's distinction between necessary causality and free causality, meaning between determinism and freedom.

12 Descartes, R. (1966). *Discours de la méthode*. Garnier-Flammarion, Paris, 47–48.

reasoning", unidirectional linear sequences, is relayed today by the preeminence given in biology to the circular causality linking in both directions two entities that are at a lesser or greater distance from each other, which complete or modify the direct linear causality[13]. In ecology, this notion of circular causality was proposed for the first time (by Hutchinson in 1948) without the specific connections with the principles of cybernetics that were developed in the same era by N. Wiener having yet been established. This *circular causality* takes on different forms up to the remarkable existence of loops (e.g. metabolics) or open circuits such as those in the *hypercycle* by M. Eigen. It is clear that currently the notion of causality must be designed as much as possible in the context of networks, meaning directed graphs connecting various elements that participate in the same type of process (see Chapter 3).

In a general manner, it is sensible to connect these considerations to the usual and still relevant distinctions accepted since the time of Aristotle between various types of causality[14], in particular the efficient cause and material cause. This distinction has been taken up by the bio-theoretician R. Rosen (see section 3.12.2) in applying it to the classic representation of a biological process with the aid of a dynamic system, meaning a set of differential equations differentiated by time, $dy(t)/dt$, expressing the speed of the aforementioned process. A speed equation corresponds to an efficient (or formal) cause, since its formalism directly determines the advancement of the process. Now, this also depends in general on the initial conditions $y(t = 0)$, where these can have a greater or lesser influence on the dynamic of the process. Let us specify, without waiting for later developments, this question of dependence with respect to the initial conditions by highlighting that it cannot be strictly quantitative by simply modifying the order of magnitude of the final state. It can also be qualitative. Indeed in certain cases, the initial state can condition the very type of dynamic as the evolution towards a particular "basin of attraction" (case of multistationary systems). This is, for example, the case for certain phase transitions, like in plants the maintenance of a meristem in a vegetative state versus its evolution towards a reproductive state (no longer generating leaves but flowers instead). The initial state then does indeed have the meaning of a cause, known as a matter cause. This means distinguishing, by analogy with mechanics, the movement of a body determined by a formal cause (its speed equation) and by its presence at the initial time (*material cause*). For a cell

13 Concerning this question, refer, for example, to Mossio, M., Bich, L. (2014). Biological circularity: concept and models. In *Modéliser et simuler*, vol. 2, Varenne, F., Silberstein, M. (eds). Éditions matériologiques, Paris, 137–169. The general theme of causality was the subject of a thematic school of thought within the CNRS (French National Research Institution), entitled "*Corrélation, causalité et régulation en biologie*", Île de Berder, 2013.

14 The four types of causality according to Aristotle are the causes known as "material", "formal", "efficient" and "final".

growth process, we have something equivalent when we distinguish between generation (local mitotic activity that generates a new cell of a given size and in a given state) and increases in size (subsequent activity of elongation of the wall).

Apical growth of a mycelial or algal filament if a good illustration of this, since the sub-apical cell can, depending on its initial state (independent of other causes), either grow without differentiation and participate in extension of the filament in the same direction, or be at the origin of a morphogenesis by budding and generating a lateral offshoot (ramification).

In the elucidation of the relationship that is required to exist between two phenomena and which can be considered to be of a causal nature (and not simply a correlation), two concepts need to be mentioned due to the epistemological importance that they had or still have in biology: vitalism and teleology. We have seen them, albeit in an exaggerated manner, as past obstacles to biology reaching a status of science that can be compared to physics[15]. It rather appears to us that they simply reflect the difficulty of agreeing on the very notion of life.

1.1.1. *Vitalism*

By vitalism, we mean a position of principle that aims to make a fundamental distinction between living things and physical material objects. For Descartes, for example, a living organism is nothing other than a machine, where no difference is seen between living matter and matter known as "inanimate". On the other hand, vitalism considers that living matter has specific properties that cannot be reduced to the set of physico-chemical elementary mechanisms, from which we deduce that they must result from the existence of a "life force" (*vis vitalis*) that is specific to it.

In principle, this concept dates back to Aristotle, with his definition of living bodies (*On the Soul*, volume II, 1). By "life", he clearly meant "the fact that they feed, grow and decay *by themselves"* (our emphasise). He thus expressed a principle of autonomy as a fundamental characteristic of life, meaning something intrinsic that inanimate bodies do not have. In a way that is more practical than philosophical, the idea of vitalism was laid out by Galen (129–~200). According to him, the study of structures and functions cannot be separated from the notion of utility as the very objective of life[16]. It somehow combines determinism and finality. Following this, vitalism was illustrated in different ways, in particular by the embryologist H. Driesch (1867–1941) in terms of the theory of epigenesis, in contrast

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15 Mayr, E. (2004). *What makes Biology unique?*. Cambridge University Press, Cambridge.
16 Galien, C. (n.d.). *De l'utilité des parties du corps humain*. See Pichot, A. (1993). *Histoire de la notion de vie*. Gallimard, Paris, 130 *sq*.

to the idea of preformation. The philosopher H. Bergson (1859–1941) actively participated in this movement in his relationships with evolution. His expression "vital impetus" (*élan vital*) means the existence of a metaphysical principle that is established at the very origin of life, the principle of "given once and for all", which then maintains itself as a connecting link between generations (*L'évolution créatrice* (Creative Evolution), 1907). In this concept, H. Bergson sees, in his own terms, "a limited force, that always seeks to surpass itself, and always remains inadequate at the work that it attempts to produce"[17].

If the existence of a vital impetus cannot be demonstrated as a defined and manipulable entity, the debate about vitalism allows us to shed light laboriously on the requirement that living mechanisms should not be limited to just the elementary laws that govern physico-chemical phenomena. Thus, with C. Bernard, whose dialectics are known, we can reject the idea of a vital principle whilst conceding alongside him that "It is obvious that living beings, by their evolutive and regenerative nature, radically differ from non-living entities, and in this respect, it is necessary to agree with vitalists"[18]. The doctor and contemporary philosopher G. Canguilhem follows the same path.

Let us explore this question of vitalism a little by noting an important point that came to light when we became aware that there was definitely a "living thing-environment" set that could constitute a particular significant entity, a "totality", the terms of which cannot be dissociated in the study of certain phenomena. The biologist J.J. von Uexküll (1934) created the term *Umwelt* to designate the behavioral environment specific to an organism[19], which needs to be distinguished from the strict topographical environment. Each organism has an environment that is well specified *lato sensu* with which it is in a close relationship. Although this concept usually refers to the sensory environment of animal species, from an ethological point of view, it is necessary to extend it to the study of other organisms where we know that various tactisms and tropisms occur, as necessary constitutive deciding factors of their environment.

Let us note that this is part of a wider set of considerations about the lack of reproducibility of the dynamic of a given process when moving from an *in vitro* experimentation to a more integrated *in situ* study. An example is given to us with

17 A comment is made about this by P.-A Miquel (Miquel, P.-A. (2007). *Qu'est-ce que la vie ?*. Vrin, Paris), who insists on two points: (i) life is power: "it is made by it"; (ii) and yet it is "inadequate for its work" since it is subject to a limit that is essential (internal) and non-accidental in nature.

18 Bernard, C. (1867). *Rapport sur les progrès de la physiologie en France*. Imprimerie impériale, Paris.

19 Refer to Canguilhem, G. (1980). *La Connaissance de la vie*. Vrin, Paris, 143 *sq*., who underlines the similarities with *Gestaltheorie*.

the case of plant cell growth (see Figure 3.11). Indeed, control of parietal extension leads to intervention *in situ* of the electrostatic potential of the wall, because this modulates the affected enzyme kinetics in terms of their microscopic properties exhibited *in vitro* (and qualified as intrinsic). It is clear that these are not sufficient for a correct representation of the dynamics of the growth process[20]. More generally, therefore let us say:

PROPERTY.– The determining set of interactions of a biological system with its environment constitutes an original characteristic of living things. This systemic view of nature is specific to biology, without an equivalent in physical sciences. In other terms, this is the question of the existence of a fundamental environment: dependence that is continuously in place in all ontogenesis.

With this mindset, the biologist R.C. Lewontin talks about a triple helix, a metaphor that is intended to outline, as if on an equal footing, a triple determinism: genome, organism and environment[21].

1.1.2. *Teleology*

Teleology can be defined as a study of the finality that can be attributed to any phenomenon. It lays down the principle of the existence of "final causes", using Aristotle's distinction between the existence referred to in the above of several types of causality, in particular an efficient or immediate cause (a phenomenon that produces another) and final cause (objective of the action). Obviously, we can reason in a consciously anthropomorphological manner, saying that having an objective constitutes in itself the determinism of all actions. More simply, looking here from the point of view of the "economy of life", we will say that it comes down to asking the question (for coherence reasons, inescapable): "What is the use of this?". Otherwise expressed, it is a case of elucidating what the "relationships between means and ends"[22] are, and not becoming fixed on just the "common sense" that says it is possible to predict the present from the past (that is known), but not the future (that remains unknown), meaning that the cause precedes the effect.

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20 Ricard, J. (1990). Le fonctionnement des enzymes en milieu cellulaire. *La Vie des Sciences*, 7(3), 197–218.

21 Lewontin, R.C. (2003). *La Triple Hélice: les gènes, l'organisme, l'environnement*. Le Seuil, Paris. Lewontin's book refers to the genetics of populations and the theory of evolution, and his research is marked by its use of mathematical formalism whilst developing its own philosophical thinking.

22 According to the definition in Lalande, A. (1968). *Vocabulaire technique et critique de la Philosophie*. PUF, Paris.

Teleology often has bad press amongst biologists, despite the essentially metaphorical nature of this term. In terms of evolution, talking about teleology comes down to attributing an objective to a particular set of evolutive processes. Thus, concerning the formation of organic structures that provide vision, from initial rudimentary photosensitive elements to the complex eyes of superior animals, it can be said that "the eye is made for you".

On this point, C. Darwin himself recognized that it was absurd to believe that the eye, with all its adjustment devices, was able to form itself solely through natural selection via a series of evolutive processes. From the teleological point of view, this evolutive convergence must be interpreted in fact as an optimization of the function of vision. Ontologically, the principle of teleology means that the development of a living thing, from an embryo to an adult state, has no "objective" other than compliant production of physiology and morphology that are characteristic of the species in question, adjusted to a lesser or greater extent by environmental constraints (morphogenetic plasticity). Anything that is simply a tautology obviously disappears and presents a problem when we look at how this remarkable production functions, with its certain stability or property of invariance.

Opposition to the very idea of teleology consists of refusing a final cause that would have an explanatory value for life processes[23]. Certain biologists wanted to rid themselves of this cumbersome term with a finalistic connotation by talking instead about "teleonomy". In fact, this changes nothing in the essence of the debate since the two terms have the same etymology (*teleos* = purpose, objective). This designation of teleonomy was proposed in 1958 by the biologist C.S. Pittenburgh who worked on the circadian rhythms of drosophila. It was taken up by the neo-Darwinist E. Mayr, who defined it as an unintentional outcome ("non-purposed end-seeking process"), an expression that is very difficult to define. Excluding any quibbles from a language point of view, F. Jacob and J. Monod use this term to mark out the principle of final cause by laying down a new founding principle: living things are "objects equipped with a project". In place of the principle of an explicit final cause, we therefore substitute the idea of a program or a series of determining instructions which link structure and function.

F. Jacob insists particularly on this new concept of program that he sees as the possibility of getting rid of old notions of finality and mechanisms. Moreover, he notes (*The Logic of Life*, p. 18) that the idea was already implicitly present in C. Bernard, whom we partially quote below:

23 Of course, here we are not referring to the idea of "intelligent intent" in the sense that a point of view of a metaphysical order does not arise from this current research.

> "There is something like a pre-established intent of each being and each organ, so that if, considered in isolation, each phenomenon of the economy is a tributary of the general forces of nature, taken in its relationships with the others, it reveals a special link, it seems directed by some invisible guide in the road that it follows and brought to the place that is occupies"[24].

Of course, in his era, these terms like "pre-established intent" and "guide" thus laid down had to appear in a teleological manner. But we know that the dialectics of C. Bernard led him to admit pragmatically, and also with a sense of nuances that is sometimes fortunately missing from the discussions, that contradictory positions exist (see Chapter 3).

A new debate begins concerning the notion of a "program" which, with its connotations of data processing, has the meaning of an algorithm that codes and assembles the basic information obtained by molecular biology. On this point, advances went up to the point of saying that the keyword of biology was no longer "organization" or "organism", but "information". "Besides the notions of energy and mass in physics, reaction and stereospecificity in chemistry, biology used from then on words of information technology and programming[25]". In any case, to remain as close as possible to the notion of causality that we are discussing, let us say that if the gene *lato sensu* can be a direct cause producing a given effect, it does so in the form of a coded instruction or program procedure. We will come back to this duality.

This epistemological evolution leads to the consideration that the originality of living things, in comparison with inanimate things, lies in the existence of a kind of double causality: every biological process is subject to specific quantitative laws (just like any physical phenomenon) at the same time as being determined and controlled by genetic programs. However, and without waiting for our later remarks on the notion known as the "complexity" of biological processes, the question is not closed, because the very term causality should be explained due to another important characteristic of biological phenomena; their variability, whose properties we must examine.

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24 Bernard, C. (1879). *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux*, t. 2. Librairie J.-B. Baillère et fils, Paris.

25 Maurel, M.-C., Miquel, P.-A. (2001). *Programme génétique: concept biologique ou métaphore ?*. Éditions Kimé, Paris, 41.

1.2. Variability in biology

We first note the underlying difference that exists between a chemical species, easily manipulated and reproducible in an identical manner, and a biological species, an entity that even in the simplest cases of genetic lineage has a random part, including the fact that the genome is not strictly invariant from one individual to another within the same species. A precise example is that of the immunological characteristics of allotypes and idiotypes concerning the individual specificity of immunoglobins, or even the existence of blood groups in mammals. On the other hand, we know of the importance of randomness in certain biological phenomena, such as sexual reproduction (e.g. the random nature of pollination in allogamous plants), occurrence of mutations, replication errors in the genome or even chromosomal crossing-over.

Due to the importance of this notion of variability, we must specify the meaning of this term, which is used in varied situations. Depending on the case, we can consider it from an ecological and phylogenic point of view or, on the contrary, envisage it in relation to the ontogenesis of a given species. On this last point, we know that certain macroscopic characteristics of an organism present themselves as a matter of fact as random variables. For example, for a given plant species and cultivar, the number of metamers of a stem of an annual plant obtained at the end of development can vary significantly within the same population. On the contrary, although the cases are quite rare, this number is obviously constant in certain highly selective species. We observe, for example, in wheat, that the main stem includes seven internodes, with little variation of this number, but this is not repeated on the organism itself in its entirety including branching. Another example in this order of ideas is that in *Arabidopsis thaliana*, the model plant of molecular biology, on certain mutants and for a given light, a constant number of leaves are generated before floral induction. Another aspect, at the scale of a population, is that the statistical variability of the size of a given organ does itself vary during growth. For example, the length of the hypocotyl (= 1st internode of seedling) presents a coefficient of highly fluctuating variation (standard deviation/average). Therefore, in the papilionaceous plant *Lupinus albus*, this statistical index fluctuates from 5 to 60% depending on the stage of growth.

We can currently specify various elementary causes of variability. Let us summarize the two microscopic levels where they take place. An initial source consists of the spontaneous and random occurrence of genetic mutations (local alterations in the sequence of nucleotides that have repercussions in the metabolic functions that follow). These are alterations of a qualitative nature, considered to be independent one after the other without an adaptative value. On the same subject, another cause of variability lies directly in a stochastic expression of genes.

The existence of random phenomena here has the complete properties of a noise, in the sense that it is a case of quantitative (and not qualitative) temporal variations of proteosynthesis.

A second type of variation is added to this, known as "epigenetics" since it occurs outside gene determinism. We know that this genetic/epigenetic distinction is delicate. Effectively, since the discovery of the lactose operon (see Chapter 3), meaning a set of genes that intervene for the same metabolic function, the idea of the existence of interactions between genes and genetic regulation networks has emerged. The term epigenetics needs to be reserved for something else, in particular the modification of chromatin (DNA-proteins association) by methylation of histone proteins. Such changes, which are indeed epigenetic in nature since they operate outside the genes themselves, are not fixed, whereas mutations are stable modifications subject to the phenomenon of heredity. To widen this table of causes of variability, let us mention, at another level, the intervention of randomness in certain enzymatic reactions, like in the case of reactions with two substrates without privileged fixing of the enzyme onto one of them.

From a more general point of view, the significance of biological variability was well elucidated in its time by the zoologist and biometrician G. Teissier[26], based on his research using cultures of micro-organisms *in vitro* in controlled experimental conditions. Whilst this type of rigorous experimental protocol allows fluctuations from one test repetition to another to be reduced, it allows significant variability to persist as something that is, let us say, "intrinsic" in nature. It is not simply a question of precision of physical measures, but of the existence of a large number of factors, of which the experimenter can only take into account a very limited number. Therefore, let us imagine the well-known difficulty of an exact reproducibility of biological tests, because mastery of operating conditions is never total. A very small change in an experimental protocol, which can even take place without the experimenter's knowledge, can significantly modify the result, a result of the sensitivity of a living thing to its environment, to which it adapts, and due to which it modifies its response to a greater or lesser extent.

We encounter this type of question when we resort to mathematical models of test plans (experimental designs) (Chapter 3). These are always stochastic models whose random parts represent all factors that are unknown and those that cannot be controlled in experiments, without necessarily relating them to the uncertainty of measurements.

26 Teissier, G. (1936). La description mathématique de faits biologiques. *Revue de métaphysique et de morale*. 43(1), 56–58.

Currently, the question of biological variability is asked in a more precise manner by considering both time and the various levels of organization. This multi-scale temporal approach is particularly interesting in development biology. For example, during early development of sea urchins, which is one of the organisms that has been well-researched with this in mind, inter-individual variability of the dynamic of cell proliferation varies according to the scale considered, high over the entire population and lower amongst groups of cells of the same type and of the same generation[27]. This being so, we will return to and develop the principle of stratification that is well known in population statistics.

Whatever the source of variability from amongst the summary that we have just done of it, the part played by random nature in living things is incomparable to its situation in the physical world, where research on it constitutes the well-outlined field of physical statistics. We recall that this developed from the kinetic theory of gases in light of the macroscopic description of a set of many microscopic constituents with random behavior (molecules, atoms, ions and particles) (refer to the example of Brownian motion).

It follows that biology can scarcely be said to have a set of duly inventoried laws that are analogous, in their rigor and in the outline of their field of action, to that of physics. Nevertheless, we will see some remarkable cases of biological laws (Chapter 4).

But other considerations need to be taken into account to understand how this intrinsic variability affects the perception that the biologist has of living things, thus entailing close interest in the relations between biology and mathematics. Essentially, as mentioned previously, it is the case that objects and biological processes are generally time-dependent, on the one hand, and environment-dependent, on the other. Let us detail a little further what this entails.

1.2.1. *Time-dependence of biological processes*

At any organizational level that we choose to place ourselves, all processes that take place in living things present this characteristic. Let us give some convincing examples of this outside the realm of evolution where, by definition, biology is a historical science.

Dynamics of living things are never strictly punctual. We see this, at a molecular level, with homeostatic variations of the internal environment, generally subject (except for all pathologies) to fluctuations over the course of a nychthemeron

27 Refer to Villoutreix, P. (2014). Vers un modèle multi-échelle de la variabilité biologique. In *Modéliser et simuler*, vol. 2. Varenne, F., Silberstein, M. (eds.). Éditions matériologiques, Paris, 660 *sq*.

(e.g. variations in glycemia), in such a way that it is more exactly a case of *homeodynamics*. This made C. Bernard mistrustful of average statistical values, because they were hiding variational properties that should not be neglected. Chronobiology came to life on the basis of this banal statement. More generally, this corresponds to the following characteristic dynamic of a living thing:

PROPERTY.– Independent of the fluctuations in the environment, there are relatively few punctual attractors that lead to a unique stable stationary state, but more often cyclic attractors (e.g. a limit cycle), where these can themselves fluctuate ("strange attractors"). Added to this there is the case of multistationary systems, for which there is a possibility of bifurcation or a qualitative change of dynamic.

Although dynamic properties of this type are not specific to biology (e.g. the chaotic dynamic of physical complex systems), we can state that physics concerns bodies or objects that are invariant with respect to time, with the exception of the well-described phenomena of hysteresis (memory), relaxation or radioactivity. This was highlighted by the physician Delbrück when he took an interest in genetics, declaring himself surprised to observe the absence of "absolute phenomena" in biology where, he noted, "everything depends on time and place".

On the other hand, at different organizational levels, living things are constantly subject to molecular (metabolic *turn-over*), cellular and organic (regeneration) processes of renewal or repair. An analogous behavior is demonstrated in the dynamics of populations and ecosystems, in particular with genetic mixing in meiosis (mitosis of sexual cells going from a ploidy of $2n$ to n chromosomes) and therefore the dynamic of genotypes within a given species.

Plants make up a very remarkable case which, even in annual species, are generally subject to continuous embryogenesis throughout their existence by maintaining meristematic activity (generation of new metamers by different buds, formation of conducting tissues by the cambium of roots and stems). These processes of neoformation are associated with diverse renewals of tissue and organics (sclerosis of old wood or duramen, replacement following natural abscissions, leaves and branches, morphological reiterations in arborescent species). Thus, we can state that the life of a plant is confused with its growth[28], and that the higher plant must be seen as a metapopulation. Development of certain organisms in colonies (such as corals) is another example of this, as well as, more generally, the process of aging and death, where the latter is consubstantial to life[29].

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28 According to the expression by Hallé, F. (1999). *Éloge de la plante*. Le Seuil, Paris.

29 The famous definition by M.F.X. Bichat (1799): "Life is the set of functions that resist death" was reviewed by H. Atlan (1979), for whom life was characterized by "functions capable of using death".

Underlining these characteristics of time-dependent biology will lead us to mention the notion of time in biology, with the search for a time described as biological (Chapter 5), different from sidereal time.

1.2.2. *Environment-dependence of biological processes*

In addition to this dependence on time and on the past, objects and biological processes are, we have said, under the influence of their environment in the wider sense of the term. This is demonstrated in the property of adaptation that is so characteristic of living things. By "adaptation", we mean the operational adjustment, both morphogenetic and physiological, to fluctuations of the environment. We will talk about this in the context of the autonomy of living systems, which is found just as much in the being ("self") as in the surrounding environment.

The idea of an influence of the environment on living things is often attributed to Lamarck who believed that he saw in this the basis for inheritance of acquired characteristics. In fact, the role of the environment dates back to I. Newton, with the former physical concept of ether, whereas for R. Descartes, for example, the notion of the environment does not exist, and all physical action comes from direct contact. For I. Newton, ether places various objects in continuity. He attributed the understanding of the physiological phenomenon of vision to it. He considers in fact that ether is "continuously in the air, in the eyes, in the nerves, and until then in muscles"[30]. It is the environment that allows a link of dependence to be set up between a light source and the movement of muscles. Subsequently, G.-L. Buffon continued this explanation, mechanical in nature, in the relationships of every living organism with its environment, then J.B. de Lamarck (who was a pupil of G.-L. Buffon and a private tutor to his son) took it up in turn by talking about "influential circumstances". Multiple well-documented cases of physiological adaptation highlight this truism of the need for this property in order for life to be maintained.

30 Canguilhem, G. (1980). *La Connaissance de la vie*. Vrin, Paris, 131.