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Jacques Monod – A theorist in the era of molecular biology / Un théoricien à l'ère de la biologie moléculaire

Why did Jacques Monod make the choice of mechanistic determinism?

Pourquoi Jacques Monod a-t-il fait le choix du déterminisme mécaniste ?

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ABSTRACT

The development of molecular biology placed in the foreground a mechanistic and deterministic conception of the functioning of macromolecules. In this article, I show that this conception was neither obvious, nor necessary. Taking Jacques Monod as a case study, I detail the way he gradually came loose from a statistical understanding of determinism to finally support a mechanistic understanding. The reasons of the choice made by Monod at the beginning of the 1950s can be understood only in the light of the general theoretical schema supported by the concept of mechanistic determinism. This schema articulates three fundamental notions for Monod, namely that of the rigidity of the sequence of the genetic program, that of the intrinsic stability of macromolecules (DNA and proteins), and that of the specificity of molecular interactions.

RÉSUMÉ

Le développement de la biologie moléculaire a mis au premier plan une conception mécaniste et déterministe du fonctionnement des macromolécules. Dans cet article, je montre que cette conception n'était ni évidente, ni obligatoire. En prenant Jacques Monod comme cas d'étude, je détaille la manière dont celui-ci s'est progressivement détaché d'une compréhension statistique du déterminisme pour finalement soutenir une compréhension mécaniste. Les raisons du choix fait par Monod au début des années 1950 ne peuvent être comprises qu'à la lumière du schéma théorique général soutenu par le concept de déterminisme mécanique. Ce schéma articule trois notions fondamentales chez Monod, celle de rigidité du déroulement du programme génétique, celle de stabilité intrinsèque des macromolécules (ADN et protéines) et celle de spécificité des interactions moléculaires.

1. Introduction

It is known and acknowledged that molecular biology was developed on a specific metaphysical basis since the late 1940s and early 1950s. Molecular biology is often and rightly depicted as a modern expression of mechanism [1],

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i.e. a long-standing philosophical and scientific movement that started to emerge in the 17th century and is characterized by a repudiation of final causes and a strong commitment to reductionism and determinism [2]. Most of the literature devoted by historians and philosophers of science to the setting up of molecular biology ordinarily focuses on the issues of mechanism and reductionism [2,3]. Until now, less attention has been paid to the issue of determinism. Moreover, most, if not all the narratives picture, at least implicitly, molecular biology as being in more or less direct continuity with mechanistic research programs that were developed at the very beginning of the 20th century, such as Jacques Loeb's [2]. From René Descartes to Emil du Bois-Reymond, and Jacques Loeb to Jacques Monod, historical lines are expected to exist, even if they are certainly tortuous. Finally, it appears that the deterministic view of classical molecular biology has recently been challenged, both by scientists and philosophers of sciences [4].

For historical, philosophical and scientific reasons, it is thus necessary to reconsider the understanding of mechanistic determinism that was – and still is – at the root of molecular biology. Taking into consideration the way in which Jacques Monod conceived molecular determinism, this paper is a contribution to such a critical examination. More specifically, the aim of this article is to show that, at least in Monod's case, the support to a strong ontological molecular determinism was not at all obvious, but was indeed the final result of a sequence of complex choices made progressively at the end of the 1940s and the very beginning of the 1950s. For Monod and what is usually called the "French school of molecular biology" [1] (which includes people like André Lwoff, François Jacob, Élie Wollman, etc.), there is no such thing as a historical continuity between their mechanistic and deterministic views of molecular working of living beings and previous forms of biological mechanisms.

I begin by advancing a thorough understanding of the concept of molecular determinism elaborated by Jacques Monod in close collaboration with François Jacob during the 1950s. This concept always articulated three main characteristics ascribed to molecular processes: their rigidity, stability, and specificity. I argue that it is only in the light of this general schema that one can truly understand what Monod and Jacob had in mind when they referred to molecular determinism. I then explore the period that I have called in a previous treatment the "Monod before Monod", from 1933 up to the late 1940s [5]. I attempt to show that during his first fifteen years as a biologist, Monod was strongly opposed to any kind of mechanistic determinism and, in contrast, understood macroscopic regularities of living beings as the final outcome of statistical laws. Finally, I address the issue of the reasons that led Monod, during the early 1950s, to abandon his statistical understanding of biological determinism and to adopt the exact opposite conception. These reasons can only be highlighted if one has in mind the general schema proposed in the first section: Monod required molecular processes to be rigid, stable and specific, and that is why, in the first place, he promoted the concept of molecular determinism.

2. What concept of molecular determinism?

Like the concepts of reductionism and mechanism, the one of determinism is a very vague one, and could refer to a large set of meanings depending on the context in which it is used. It is therefore very difficult to examine what scientific determinism in general is, even when one wishes to consider only a specific area of science. In a recent work, Daniel Nicholson has claimed that in biology, the word "mechanism" could have at least three very different meanings [2]. The polysemy of the word "determinism", even restricted to the field of the life sciences, is at least equivalent.

Nevertheless, in molecular biology, this word seems to have a quite specific sense, which could be defined explicitly and rigorously. In their own writings, Monod and Jacob often associated the idea of determinism with the one of molecular mechanism, where mechanism is understood in the sense of *machine mechanism* as defined by Nicholson, i.e. "the internal workings of machine-like structure" [2 (p. 153)]. Monod and Jacob thought of the organism as a complex machine, in which each molecular piece has a specific structure in relation to a particular function. The good working order of the entire organism results as the deterministic summation of the functioning modes of its molecular parts. Such a conception is obvious and transparent in Monod's and Jacob's famous books published in French in 1970, namely *Chance and necessity* and *The logic of life*, respectively [6].

This general view, which closely links machine mechanism and determinism, is consubstantial of the setting up of molecular biology and has remained prevalent until nowadays. Taking into account the way Monod and Jacob themselves used to present their own ideas, it is possible to provide a definition of the concept of mechanistic determinism that was pivotal in the birth of molecular biology. The definition I propose is the following: molecular mechanistic determinism (MMD) is *the postulation of a mechanical and causal relation between individually characterized molecular surfaces of nanometric scale*.

The definition proposed emphasizes two crucial aspects of the concept of MMD. The first is that this determinism is ontological, not epistemic. The second is that it is a microscopic determinism. It means that most molecular biologists assumed that, in the main, molecular structures do behave like microscopic machines acting in a deterministic way. In *Chance and necessity*, Monod explicitly pictured the cell as a Cartesian clock machine mechanism, cogs of which work in a deterministic manner (cf. Section 3) [6a (p. 110–111)].

This definition of MMD is general and should not be restricted to Monod and Jacob's theoretical claims. What is specific, at least to some extent, to Monod and Jacob, is the use and purpose of the concept of MMD, as a careful examination of their writings highlights it. It is quite clear that for both of them, it was a kind of conceptual nexus that articulated and made thinkable the three major characteristics ascribed to the molecular machinery. This machinery was supposed to possess rigidity, stability and specificity. Most of the time, rigidity was associated with the course of the genetic program, stability was seen as a property of DNA and proteins, and specificity concerned the nature of molecular interactions (see Fig. 1). For example, Jacob expressed the rigidity of the genetic program as follows:

> "The aim of modern biology is to interpret the properties of the organism by the structure of its constituent molecules. In this sense, modern biology belongs to the new age of mechanism. The program is a model borrowed from electronic computers. It equates the genetic material of an egg with the magnetic tape of a computer. It evokes a series of operations to be carried out, the rigidity of their sequence and their underlying purpose" [6b (p. 9)].

It was thought that rigidity, stability and specificity can be completely effective only if molecular processes are of the deterministic type. This complex explanatory device was prevalent since the mid-1950s in Monod's and Jacob's writings, and remained so until the end of the 20th century. In 1993, seventeen years after Monod's premature death, Jacob proposed another and updated molecular model in order to explain gene expression at the transcription level, which he called the "aggregulate" (the name was formed by a recombination between *aggregate* and *regulation*). This model stipulates that "genes have become the products of some kind of Meccano [a very common term in Jacob's vocabulary] linking together relatively short DNA fragments in which discrete polypeptidic domains or modules are coded". It emphasizes that "the 3-D shape of these modules, their electrostatic charge and their capacity of hydrophobic reactivity determine their possibilities of recognition and interactions" [7]. The aggregulate model is therefore a perfect illustration of the way in which Monod and Jacob conceived the functioning of molecular structures in terms of rigid, stable and specific interactions that are performed in a deterministic microscopic world.

3. Monod against mechanistic determinism (1933–1950)

François Jacob started his scientific career in September 1950, at the time of the birth and development of the new molecular biology [8]. It is therefore impossible to know what his thoughts could have been about the issue of determinism before he participated in the elaboration of the concept of MMD that I have just defined. Fortunately, the situation was not the same for Monod. He was ten years older than his colleague and started studying biology as soon as 1928, when he entered the Sorbonne. At the age of 23, he published the first articles of which he was the sole author [9], and eight years later, in the difficult context of the Second World War, he managed to defend his PhD thesis on bacterial growth, in 1941 [10]. In 1947, he was internationally recognized as one of the main experts in the promising field of enzymatic adaptation and published an extensive report on this topic [11]. Hence, the young Monod represents the perfect case study to understand how the concept of MMD came into being.

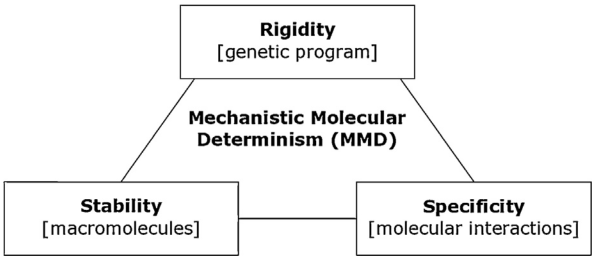

Fig. 1. The general explanatory schema supported by Jacques Monod and the French school of molecular biology. Mechanistic Molecular Determinism (MMD) was the pivotal concept for giving a theoretical basis to the notions of rigidity, stability, and specificity of the molecular machinery.

What is fascinating here is not so much that Monod was already concerned with this matter in the 1930s and 1940s, but rather that he was strongly opposed to any form of mechanistic determinism during this period. On several occasions, he explicitly stated that biological regularities were only statistical, like the descriptive laws of macroscopic physics, and that they were the consequences of the microscopic heterogeneity that takes place at the molecular level. At least for Monod, the concept of MMD, which he progressively constructed and supported during the 1950s, must be understood as a complete novelty in his way to conceive the relationship between microscopic and macroscopic events in living things.

In a previous work, I have already shown that Monod was at the beginning of his career a biometrician and should not be first considered as a biochemist [5]. His first works as an experimental biologist, from 1933 until his PhD thesis, are the ones of a typical biometrician interested in quantitative research in order to shed light on some specific processes of life. In the mid-1930s, he started studying the growth of ciliate cultures and, because he ran up against practical problems, he subsequently changed his experimental system from ciliates to bacteria. Taking into account the growth curves of different bacterial cultures, he was able to demonstrate the phenomenon of "diauxie", which finally led him to study enzyme formation and enzymatic adaptation.

It is well known that Monod became fascinated with the experimental possibilities allowed by the exponential phase of bacterial culture growth [10 (pp. 16–17)]. He liked to compare such a system to a perfect gas. Individual peculiarities did not matter, and only population characteristics were relevant in order to establish the scientific laws of nature. Through a quantitative approach, Monod's ultimate goal was to physicalize biology [12], and because the new statistical understanding of physics opposed any kind of mechanistic determinism, Monod first wanted to transpose this epistemology in the field of biology.

Monod's interest and preference for a statistical understanding of biological laws and regularities is clearly shown on at least two occasions. The first is the publication, in 1947, of his famous text entitled "The phenomenon of enzymatic adaptation, and its bearings on problems of genetics and cellular differentiation". At the end of this 66-page report, Monod proposed, for the first time, a model in order to explain ontogenesis. He first gave up the idea that enzymatic adaptation could be a key phenomenon in embryogenesis because it causes only temporary modifications, whereas embryological development requires permanent modifications of the cell's potentialities. He then quickly set forth the main lines of a new model based on microscopic heterogeneity. He conceived embryogenesis as the macroscopic consequence of a Darwinian mutation/selection process that takes place at the cellular level during the late stages of development, when the number of cells in the embryo is already large enough to make such a statistical phenomenon possible [11 (pp. 284–286)]. In its general sense, this model is very close to current ideas that identify embryogenesis as the result of the stochastic activation of genes followed by selective processes [13]. These models were recently developed to offer an alternative to the paradigm of the deterministic genetic program, i.e. the generalization of Jacob and Monod's ideas that were first published in 1961 [14]!

A few months after Monod published his first model of the mechanism of embryogenesis, he became one of the main French protagonists in the "Lysenko affair". In France, the Lysenko affair really began at the end of the summer of 1948. On 26 August, Jean Champenoix published, in the French journal *Les Lettres françaises*, an article that was more or less an apology for Lysenko's new biology [15]. His arguments were entirely political and ideological. Another journal, *Combat*, asked four scientists to analyse Lysenko's scientific claims: Jean Rostand, Maurice Daumas, Marcel Prenant, and Jacques Monod. Monod's text, the last one, was published on 15 September and its title allowed no doubt about the complete opposition of his author to Lysenkoism: "The victory of Lysenko is completely without scientific foundation" [16]. Monod emphasized the fact that Lysenko was able to control Soviet biology not because his "science" was theoretically and/or empirically superior to western science, but only because of its perfect fit with the Marxist ideology of dialectic materialism.

Monod was so affected by the Lysenko affair that he decided to produce a detailed scientific, ideological and political evaluation of Lysenkoism. During the next few months, at the end of 1948 or in the course of 1949, he wrote, in French, two unpublished and undated texts on the doctrine of Lysenko. The first one is an 8-page manuscript entitled "Mechanics and statistics" (see Fig. 2) [17], whereas the second one is a 68-page typescript written in three bouts [18]. Both of them tackle the question of the nature of scientific laws because Lysenko blamed genetics for being only a statistical science. Monod's argument was that scientists, and especially physicists, are now well aware that every general law of nature is only statistical:

> "It is utterly useless, I believe, to retrace here the history of Science for a hundred years, to show how the calculation of chance took a more and more important place there, and why the scholars were brought to recognize, not only that *all* their knowledge, all their observations were of statistical order, but still that almost all the laws, even the most rigorous, express in reality *not certainties*, but probabilities" (ibid [9], p. 15, my translation).

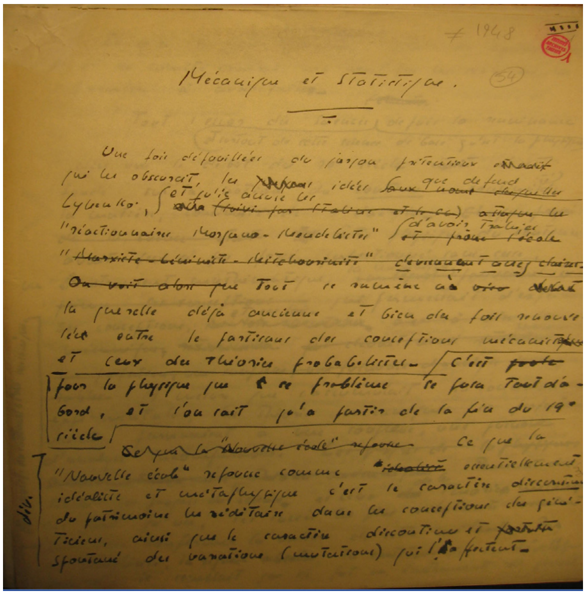

Fig. 2. (Colour online.) First page of an unpublished manuscript written by Monod in 1948 or 1949 (Archives of the Pasteur Institute, Paris). In 1948, Monod opposed the old mechanical conception of science (like the one promoted by Lysenko) to the new statistical understanding developed since the end of the 19th century.

These two texts perfectly show that Monod was at this time convinced that the classical mechanistic metaphysics had become irrelevant, and that a statistical conception of the physical world was more appropriate. In these texts, he pictured the Lysenkists as "the partisans of the mechanistic conceptions" and the geneticists as "the one of the probabilist theories" [18 (p. 1)]. To him, there was no doubt that only the latter could be the basis of a fruitful understanding of complex biological processes. These examples are thus consistent evidence supporting the claim that Monod, still at the end of the 1940s, was much more interested in a statistical understanding of the concept of determinism than in a mechanical one. If that is true, it means that during the 1950s, Monod completely changed his mind on that important issue.

From a more general perspective, it is important to notice that most of the biochemists of the interwar period favoured a dynamical view of the molecular working of the cell. It was assumed that, inside the cytoplasm, molecules and especially proteins were integrated in complex cycles and were thus continuously transformed. The biochemist Rudolph Schoenheimer, who developed the technique of isotope labelling of organic molecules during the 1930s, promoted a general view of the cell as a dynamic entity, where constituents are in a constant state of chemical renewal. As he expressed in his famous 1942 book (*The dynamic state of body constituents*), this point of view was in opposition with the classical view of an organism as a rigid machine:

> "For the few coupled biochemical reactions which have been carefully investigated, such as those involved in muscle contraction or respiration, it has been shown

that every chemical step is specifically related to some other. The complex organic molecules present in living matter must require for their maintenance the steady occurrence of an abundance of various reactions. The finding of the rapid molecular regeneration, involving constant transfer of specific groups, suggests that the biological system represents one great cycle of closely linked chemical reactions. This idea can scarcely be reconciled with the classical comparison of the living being to a combustion engine or with the theory of independent exogenous and endogenous types of metabolism" [19].

Schoenheimer's work and ideas were very influential in the 1940s, especially for the young Monod. In his Nobel Lecture, in 1965, Monod admitted that, during the 1950s, he was finally led to "seriously question" "the dogma of the 'dynamic state'" [20].

4. The reasons of a theoretical choice (1950–1970)

At least for Monod and Jacob, the choice of a mechanistic understanding of molecular determinism must be grasped in the light of a complex theoretical device (Section 1). They both needed that kind of determinism because they both supported the ideas of rigidity of the sequence of the genetic program, of stability of organic macromolecules, and of specificity of molecular interactions. The reasons for choosing MMD must then be looked for in their attachment to the notions of rigidity, stability, and specificity. Why did Monod and Jacob find these notions crucial for the development of molecular biology?

The first set of reasons is mostly metaphysical, and concerns the idea of the rigidity of molecular operations and especially of the sequence of the genetic program. It must be emphasized at this point that classical French biology was shaped by a strong Lamarckian tradition since the beginning of the 19th century, a tradition that was still alive during the 1940s and the 1950s [21]. This long-lasting Lamarckian orientation was reinforced, since the interwar period, by a revival of vitalism, supported by scientists (Albert Vandel, Pierre-Paul Grassé) and philosophers (Bergson in the first place). Monod and Jacob were of course aware of this situation. They paid particular attention not to give any room to explanations or hypotheses that could be interpreted in Lamarckian and/or vitalist terms. This attitude was obviously strengthened by the Lysenko affair.

In *Chance and necessity*, Monod devoted a whole chapter (out of nine) to the demonstration of the failure of any type of vitalism (Bergson, Teilhard de Chardin, Marx, Engels, Lysenko, etc.). It is significant that on this occasion, his rejection of Lysenkoism was explicitly based on a mechanistic conception of the new molecular genetics, which is contrary to the arguments that he had developed against Lysenko more than twenty years before:

> "Despite the disclaimers of the Russian geneticists, Lysenko was perfectly right: the theory of the gene as the hereditary determinant, invariant from generation to generation and even through hybridizations, is indeed completely irreconcilable with dialectical principles. It is by definition an idealist theory, since it rests upon a postulate of invariance. The fact that today the structure of the gene and the mechanism of its invariant reproduction are known does not redeem anything, for modern biology's description of them is purely mechanistic" [6a, p. 40].

The rigidity of molecular operations was a way to reject the very possibility of the inheritance of acquired characters and, at the same time, to oppose any form of vitalism. To conceive embryogenesis as an inevitable sequence of events under strict genetic control was supposed to be the ultimate argument in order to defeat any form of Lamarckism. The cell was a machine, stiffened in its cogs:

> "Hence the entire system is totally, intensely conservative, locked into itself, utterly impervious to any 'hints' from the outside world. Through its properties, by the microscopic clockwork function that establishes between DNA and protein, as between organism and medium, an entirely one-way relationship, this system obviously defies any 'dialectical' description. It is not Hegelian at all, but thoroughly Cartesian: the cell is indeed a *machine*" [6a, pp. 110–111].

This metaphysical positioning in favour of the rigidity of the working of the cell supported – and was supported in return by – the notion of intrinsic chemical stability of organic macromolecules. Monod's claim for a non-dynamic view of the cell's components, i.e. molecular stability, was mostly the consequence of experimental results and new data obtained during the first half of the 1950s. In close collaboration with Melvin Cohn, Monod was able to demonstrate, using immunological techniques and radioisotopes, that the formation of inducible enzymes was a *de novo* synthesis [22]. The new enzyme was not the transformation of pre-existent hypothetical precursors, like he thought in 1947, and was chemically stable as soon as it was created.

In October 1958, Monod was invited to give a series of three conferences within the prestigious context of the Dunham Lectures. The drafts of these conferences are now stored in the Archives of the Pasteur Institute, and are very helpful in order to study Monod's theoretical reversal. The first conference was entitled "Properties, functions and interrelations of galactosidase and galactoside-permease in *Escherichia coli*". On the basis of his own experimental results, Monod expressed in very strong terms the inadequacy of Schoenheimer's ideas:

> "The 'dynamic state theory' conceived as describing an inherent and essential state of protein molecules in the cell cannot be retained. This does not apply only to proteins. The whole trend of modern molecular biology makes it every day clearer that structural stability and rigidity rather than dynamicity are the most essential and characteristic properties of the typical cellular macromolecules" [23].

In a more significant way, Monod took advantage of this lecture to clearly take a stand in favour of a deterministic and mechanistic conception of the molecular world, and to dismiss the statistical conception that he had previously defended:

> "Thus, the protein-synthesizing process appears to work with very high precision, and the concept of molecular micro-heterogeneity due to errors or fluctuations in this process appears unwarranted. Putting it otherwise: even in the formation of such a very large and complex molecule, the synthesizing system appears to work mechanically, like a clock or a precision machine tool, rather than statistically (like what?) (Schrödinger)" (ibid [23], pp. 12–13).

The reference to the physicist Erwin Schrödinger is meaningful here. A few pages further, Monod praised him as a "genius", because of the predictions he was able to make in his famous book *What is life?*. Monod was particularly impressed by the fact that Schrödinger, as soon as 1944, defended the idea that the hereditary material must have two crucial properties, "rigidity" and "stability" (ibid [23], p. 29). However, Schrödinger's influence on Monod should not be limited only to the matter of the intrinsic stability of DNA and proteins. It is well known that in his book, Schrödinger also expected new "order-from-order" laws of physics. As Sahotra Sarkar emphasized, these new laws "were not new forces but, rather, new principles" [24]. Because of this classical confusion between forces and principles, it is common to underline the failure of Schrödinger's project to reveal new laws of physics by studying molecular processes that take place inside living things. This judgement is indeed excessive and the way Monod went to conceive the essential principles of molecular biology represents a perfect example of the fecundity and of the success (at least to some extent) of the research program formulated by Schrödinger in 1944.

The third chapter of *Chance and necessity* ("Maxwell's demons") is devoted to the challenge posed by Schrödinger: how is it possible to explain the order-from-order relations that take place inside an organism or a single cell in a physical world ruled by the second principle of thermodynamics? Monod's answer is directly related to the third conceptual piece of the explanatory schema I have described in the first part of this article. For Monod, the Maxwell's devils that are involved in this biological property are precisely the proteins and their unique ability to form specific interactions between them:

> "In short, the enzymes function exactly in the manner of Maxwell's demon..., draining chemical potential into the processes chosen by the program of which they are the executors. Let us retain the essential idea developed in this chapter: it is by virtue of their capacity to form, with other molecules, stereospecific and non-covalent complexes that proteins exercise their 'demoniacal' functions" (ibid [6a], p. 61).

The specificity of molecular interactions is the key concept for producing a scientific explanation of the "negentropy" of living structures and processes. As for rigidity and stability, molecular specificity requires a complete support of the concept of MMD.

5. Conclusion

The concept of MMD was pivotal in the setting up of molecular biology during the 1950s and the 1960s. However, the Cartesian view of the cell that emerged during this period was not in direct historical continuity with previous forms of mechanism. The case of Jacques Monod shows quite the reverse, namely that MMD was elaborated against the dynamical and statistical considerations prevalent during the 1930s and 1940s. This implies that the founders of molecular biology made the choice to promote a strong understanding of MMD. Historians of science, therefore, have to look carefully for the reasons that could explain such a choice, and should not take for granted the support of the first molecular biologists to MMD.

At least for the French school of molecular biology, it is also essential to take into account not only the concept of MMD in itself, but also the complex theoretical network in which it was incorporated. MMD was the central nexus articulating the concepts of rigidity (of the genetic program), stability (of macromolecules) and specificity (of molecular interactions). That is why understanding the reasons of Monod's choice in favour of MMD means, in fact, identifying the motivations that led him to put in the foreground the notions of molecular rigidity, stability, and specificity. I have shown that these reasons were a complex mixture of metaphysical positioning (against Lamarckism and vitalism), experimental results (chemical stability of enzymes), and theoretical propositions (in the wake of Schrödinger's considerations).

To conclude, I would like to indicate that Monod's reversal in favour of MMD was not as complete as it could seem. During the 1960s and the 1970s, on some occasions, he still mentioned that natural phenomena were controlled by a statistical determinism, not a mechanistic one (ibid [6a], pp. 43–44). It thus remains an irreducible tension, in Monod's considerations and writings, between a deterministic and a statistical understanding of the functioning of the material world. *Chance and necessity* could also be read as a direct expression of this tension.

Acknowledgements

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