Monod and the spirit of molecular biology

Michel Morange

Titre : Monod, et l'esprit de la biologie moléculaire

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Auteur :
Michel Morange
USR3608 Centre Cavaillès – République des Savoirs
École normale supérieure
29, rue d'Ulm
F-75230 Paris Cedex 5
Tél. : +33 (0)1 44 32 29 61
Courriel : michel.morange@ens.fr

Résumé : Les fondateurs de la biologie moléculaire partageaient certaines vues sur la place de la biologie parmi les sciences, aussi bien que sur les relations de la biologie moléculaire avec le darwinisme. Monod ne faisait pas exception, mais l'étude de ses écrits est particulièrement intéressante car il exprime son point de vue avec une grande clarté, et pousse les conséquences de ses choix plus loin que la plupart de ses contemporains. L'esprit de la biologie moléculaire actuelle n'est plus le même que celui des années 1960, mais de manière intéressante Monod a anticipé quelques unes des évolutions récentes de cette discipline.

Mots-clés : allostérie, darwinisme, Max Delbrück, finalité, Karl Popper, symétrie, Synthèse moderne

Abstract: The founders of molecular biology shared views on the place of biology within science, as well as on the relations of molecular biology to Darwinism. Jacques Monod was no exception, but the study of his writings is particularly interesting because he expressed his point of view very clearly and pushed the implications of some of his choices further than most of his contemporaries. The spirit of molecular biology is no longer the same as in the 1960s but, interestingly, Monod anticipated some recent evolutions of this discipline.

Keywords: allostery, Darwinism, Max Delbrück, finality, Karl Popper, symmetry, Modern Synthesis

Article :

Introduction

It is not necessary to refer to the Vienna Circle to acknowledge that there is no such thing as "a spirit of molecular biology". Not only because a discipline has no spirit, but also because molecular biology was in permanent transformation, and because the molecular biology of the 1960s was not that of the 1980s or of today.

This did not prevent many of the founders of molecular biology, those who participated in its rapid development between 1940 and 1960, from sharing common ideas about the place of biology within the sciences, and the role of evolutionary theory in the explanation of biological facts. Among these shared conceptions, I will successively consider the project to "naturalize" life, the vision of physics as a multidimensional model for the biological sciences, the complex relations that molecular biologists had with Darwinism, and the evolutionary synthesis.

In most cases, the conceptions of Jacques Monod were those of the majority of molecular biologists. The clarity with which he expressed them, as well as the way he pushed them to their ultimate implications, can help to outline the "spirit" of molecular biology, as well as eventually to understand how Monod's ideas could be distinguished from those commonly held.

1. The project to "naturalize" life

Monod often stated that his motivation for doing biological research originated in the flavour of metaphysics that still pervaded biological explanations when he was a student. For him, as for many molecular biologists, natural explanations had to be found for biological phenomena, just as had been done for physical phenomena centuries before, with the rejection of the physics of Aristotle during the scientific revolution, and the theories of Galileo and Newton.

The core of the issue was the place of finality in biology. Not only did the structures of organisms seem to be perfectly adapted to the functions they fulfilled, and to the environment in which the organisms lived, but the embryological development of multicellular organisms also seemed to be directed towards an end, the construction of an adult organism belonging to a well-defined species. The first form of finalism had been attacked head on by Darwin, and the emergence of the evolutionary synthesis in the 1940s signed its death warrant among biologists. As Monod would express later, this apparent finality of the structures and behaviors of organisms is the simple consequence of the "chance and necessity" to which organisms are subject [1].

The second expression of finality, in embryological development, dates back to Aristotle, but was resurrected by the eminent German embryologist Hans Driesch at the beginning of the 20th century [2]. In experiments in which he perturbed the early phases of embryological development, he observed the extraordinary capacity of organisms to adapt to these perturbations, and to restore normal embryological development. He became convinced that the only possible explanation of this capacity was the existence within organisms of a principle that orients the developing organism towards the form that it must adopt at the adult stage, to which he gave the name of "entelechy".

The influence of Driesch had been considerable among embryologists. This was in part due to the reputation he had acquired as an experimenter, but also to the fact that the mechanisms of development were beyond the reach of the techniques and concepts available to biologists at that time. Since the time of Claude Bernard, a natural explanation for finality had been sought in the existence of regulatory mechanisms controlling the functions and the embryological development of organisms. This explains why the discovery of allosteric regulation—a process by which enzymatic activity is controlled by molecules whose structure is unrelated to that of the substrates—and the elaboration of models explaining the allosteric behavior of proteins were so important for Monod. The fact that he called the discovery of allosteric regulation that of the "second secret of life" [3]—the first being the double helix structure of the genetic material—was not a sign of pretention, but the conviction that the huge possibilities of regulation offered by allosteric regulation were precisely what had previously been missing from attempts to eject finality from biology. The value of allosteric regulation came from its partial independence of the thermodynamic relations that constrain the living world.

2. Physics as a multidimensional model

To naturalize life and biological phenomena meant mimicking what physicists have done. For that reason, and also because physics had experienced hugely successful transformations at the beginning of the 20th century—with the rise of quantum and relativity theories—and had attracted a lot of attention, physics appeared as a model for the biological sciences to follow. This was not a new phenomenon. The rise of physiology in the middle of the 19th century, and the development of experimental embryology at the end of the same century, were previous efforts to align biological sciences with physics, by shifting the activity of biologists from observation to experimentation.

The type of physics that might be useful for biologists was not obvious. Quantum theory was appealing for good, but also for bad reasons: it had successfully challenged some of the characteristics traditionally attributed to reality—such as the possibility of distinguishing the observer from the object that is observed. But a full understanding of quantum physics called for mastery of mathematical tools unfamiliar to most scientists, including many physicists and all biologists. The success of quantum physics was due to the pedagogical talent deployed by some of its protagonists to popularize it, notably Werner Heisenberg, Niels Bohr and Erwin Schrödinger. The latter two were particularly important, because they both suggested that the solution to the mystery of biological phenomena would be found in quantum physics. For Bohr this would be done by applying an epistemological principle deriving from quantum physics—the principle of complementarity. Schrödinger favored a more direct approach through description of the specific characteristics of biological components that gave them special quantum properties [4]. Both were wrong, and quantum physics has not so far played an important role in biological explanations. The branch of physics that was important for the development of the new technologies that permitted the description of macromolecules and which accompanied the development of molecular biology—ultracentrifugation, electrophoresis, X-ray diffraction—was "classical" physics, optics, mechanics. This did not prevent many young physicists, trained in the new quantum physics, from turning to biology and playing a major role in the development of molecular biology. The emblematic example is Max Delbrück (1906–1981), a quantum physicist who was convinced by Niels Bohr to orient his research towards biology after his thesis, and who played a major role in developing a simple experimental system—the bacteriophage and its host, the bacterium. This system became the focus of a large part of the young community of molecular biologists. Nevertheless, Max Delbrück always remained in search of "something else" to explain biological phenomena, and was disappointed that the genetic power of DNA could be so easily explained by its chemical structure.

We must distinguish the fact of a discipline being a model for another from the importance the first had in the scientific development of the second. In the case of Monod, who was not familiar with physics, it was his representation of physics and not physics itself that played a key role in his scientific activity, and supported his efforts to naturalize biology.

Monod made recurrent allusions to the characteristics of his own research, and to that of molecular biologists who broke with the previous habits of biologists and permitted biology to align itself with well-established practice in physics. One of these characteristics was the search for general laws, emerging from the study of a large population of objects. Monod frequently likened the culture of bacteria (*E. coli*) and of bacteriophages to perfect gases [5]. Their growth obeyed precise quantitative laws that he helped to establish and which are similar to the general laws relating pressure, volume and temperature that emerged from the study of perfect gases.

Nevertheless, this comparison is ambiguous. In physics, the laws emerged from the random interactions between individual molecules. For Monod, the use of large populations enabled inter-individual differences of no importance to be neglected, and the extraction of laws common to all organisms.

Similarly, Monod hesitated concerning the origin of chance involved in the evolution of organisms. In *Chance and necessity* [6], he rightly considered that chance is the result of the fortuitous encounter of two independent causal chains, a conception already outlined by Aristotle, but explicitly expressed by Cournot in the 19th century. But his blind admiration of modern physics led him in another part of the same book to state that the origin of chance in evolution was the uncertainty principle recently discovered by quantum physicists.

That the study of simple models was the best way to solve huge issues—for instance, the use of bacteriophages to explain biological reproduction, a choice made by Max Delbrück—was a well-accepted idea in physics, and was also obvious for Monod. He never abandoned *E. coli* to work on more complex organisms, in contrast to what most molecular biologists did after 1965. During the greater part of his scientific career he studied one single phenomenon—enzymatic adaptation—the capacity of organisms to adapt to a new nutrient, with which they have been put into contact, by producing the enzymes necessary for its degradation. Adopting the point of view of Marjory Stephenson, he was convinced that enzymatic adaptation was an excellent model for the study of cell differentiation—the acquisition during development of new characteristics by the cells of an organism. This explains why, when the operon model was produced by Monod and François Jacob to describe enzymatic adaptation (and lysogeny), they immediately modified the model to account for the changes in gene expression that occur during differentiation and development [7].

This admiration for physics explains the highly abstract form that Monod, Jeffries Wyman and Jean-Pierre Changeux gave to the theory of allostery [8]. In contrast to the American biologist Daniel Koshland, who in parallel explained the behavior of allosteric proteins by the deformations induced within the proteins by the binding of ligands [9], they proposed a very different model in which two symmetrical protein conformations pre-existed in equilibrium, and the effect of allosteric regulators was simply to shift this equilibrium. The allosteric model relied on a principle established by the physical chemist Le Chatelier at the end of the 19th century, but it added structural symmetry as an additional principle controlling the allosteric phenomenon. Physicists, and in particular those working in particle physics, had attributed increasing importance to symmetry and its conservation in their explanations in the second half of the 20th century. Probably aware of this new trend in physics through his own son, who was a physicist, Monod was happy to give to the principle of symmetry, so important in physics, a founding place in the explanation of allostery, which he considered, as we have seen, the second secret of life.

This appeal to a principle of symmetry was not understood by other molecular biologists. They preferred Koshland's more empirical induced-fit model. Some of the constraints introduced by the principle of symmetry were shown to be violated by some allosteric proteins (such as the exclusion of some forms of symmetry). The allosteric theory of Monod, Wyman and Changeux was neglected, and only recently rediscovered when newly developed technologies permitted the dynamic study of proteins, and confirmed and extended the existence of pre-existing equilibria [10].

This interest in "principles" led to a contempt for the "details" of chemical structure. No investments were made at the Pasteur Institute in favor of structural chemistry and biochemistry—a line of research brilliantly pioneered by Linus Pauling—or for the characterization of the three-dimensional structures of macromolecules by X-ray diffraction studies. Physical chemistry was preferred to structural chemistry, and within the DGRST funding program organized by the government of General de Gaulle to support research, which was so important for the development of molecular biology in France, young molecular biologists were recruited among physicists (and not chemists).

This permanent reference to physics explains some other facets of Monod's activity, less directly related to his own scientific work.

One such was his admiration for genetics, and his constant defense of this discipline. He had discovered genetics during his visit, with Boris Ephrussi, to Thomas Morgan, the father of genetics through his study of *Drosophila*, in California in 1935. Later, he isolated mutants of *E. coli* affected in enzymatic adaptation, but did not participate in the development of bacterial genetics in the 1950s, and had to seek Jacob's help at the end of the 1950s when he became convinced that the solution to the problem of enzymatic adaptation would come from the characterization of the mutants that he had isolated.

In 1948, when the communist parties of Western Europe were obliged to support the "theory" of Trofim Lysenko, and to oppose genetics, Monod reacted violently [11]. Like many biologists, including Boris Ephrussi, he was convinced of the pre-eminence of genetics among the biological disciplines, and of its resemblance… to physics [12]. Genetics was abstract, and used mathematical tools. However, its mathematical apparatus was far from being as sophisticated as that of physics! The parallel between genetics and physics was pushed further, and genes were considered as the "atoms" of biology, the foundation stones on which the knowledge of biological facts could be built.

The ambition of Monod and of many molecular biologists was also to imitate the way of thinking and working of physicists. The movement was initiated by Max Delbrück, who brought the habits of young German quantum physicists to California. It consisted of the absence of a strict separation between work and leisure, and the inclusion in scientific activity of a time slot devoted to free discussions and reflections, in which hierarchy between individuals had no place. Such a change in behavior was facilitated by the more relaxed American way of life. It also had a strong epistemological meaning: the work of biologists must not simply consist in accumulating observations, but also in organizing them in a more abstract, theoretical framework.

Monod was particularly receptive to this new mood. He had deeply suffered before the war, when he worked at the Sorbonne, from an absence of scientific contacts and discussions. This probably explains why, with André Lwoff, he encouraged highly open and friendly exchanges in the lab,

famously known as the “Le Grenier” (“The Attic”), which left a strong and lasting impression on the numerous scientists who spent some time there.
Monod also tried to transfer the epistemology of physics to biology. The philosopher of science who was the most acquainted with the recent advances in quantum physics, and who used them to elaborate a philosophy of science adapted to modern science, was the Austrian-born Karl Popper. Monod wrote a preface to the first French edition of Popper’s major work *The logic of scientific discovery* [13]. It was also a way for him to contrast this form of philosophy, useful to scientists, with “German” philosophy, and in particular phenomenology, which considered, according to the famous words of Heidegger, that “science does not think”.
Monod and many molecular biologists tried to be Popperian in their way of doing science, devising experiments likely to falsify the existing theories. Nevertheless, in an ironic cartoon representing Monod, Martin Pollock, one of his collaborators, suggested that new theories flourished more rapidly than confirmed facts in Monod’s laboratory [14]. Many discussions took place among philosophers on the value of Popper’s theory for the biological sciences. A broad consensus was reached that the limited number of theories in biology makes the transposition of Popper’s theory to this discipline problematic.

3. Complex relations with Darwinism, and the evolutionary synthesis
When questioned, most of the founders of molecular biology acknowledged the importance of Darwinian theory. Molecular biology and Darwinism had been tightly associated since the famous Luria-Delbrück experiment in 1943 demonstrating that the resistance of bacteria to bacteriophages was not due to a Lamarckian adaptation of bacteria to their invaders, but to the pre-existence in the bacterial population of rare variants resistant to them [15].
In their practice also, bacterial geneticists widely appealed to Darwinian theory, and to the creative power of natural selection, to disentangle the complex mechanisms underlying biological processes: isolation of mutants, and their characterization, were the main tools that they used.
Faced with the neo-Lamarckian spirit that still pervaded French biology, molecular biologists, and in particular Monod, were considered as representatives of Darwinism, a role that Monod did not refuse. In *Chance and necessity* [16], he described the principles of Darwinian theory, and their importance for the biological sciences. The article presenting the theory of allostery contained a part justifying its characteristics “in the light of evolution”. The argument was the following: the principle of symmetry, on which we have put so much emphasis before, minimized the number of mutations required to generate certain regulatory properties, and for this reason its emergence has been favoured by the action of natural selection. This effort to introduce an evolutionary explanation in a structural model is noticeable, but was not perceived by most observers. When the issue was to choose between the models of Koshland and Monod, no reference was made by the protagonists to the evolutionary arguments, and the only question was to determine which of the two models best fitted the data.
In Monod’s model, Darwinism is used to explain the formation of enzymes with higher regulatory capacities: natural selection is considered as a factor of progress, in what Gould and Lewontin later called a “Panglossian view” of evolution [17]. No reference is made to the fact that adaptation is always local and contextual, linked to a particular environment. The vision of evolution supported by molecular biologists including Monod differed greatly from that of evolutionary biologists as expressed in the Modern Synthesis.
There are probably two reasons for this discrepancy. The first is to be found in the traditional separation between the functional and evolutionary approaches to biological phenomena that has been particularly well described by Ernst Mayr [18]. The second is simply the common ignorance of scientists from one discipline or subdiscipline of recent developments in other disciplines and subdisciplines. The view of evolutionary theory that Monod and other molecular biologists had was a vague one. In particular, they were wholly ignorant of the developments that occurred after the establishment of the Modern Synthesis.
For evolutionary biologists, the range of possibles open to evolution is wide, so that organisms

often find ways to adapt. What is selected is a function, and many structural modifications would have been able to provide the same modification of function. This underscores that knowledge of the precise nature of mutations is not important. As already mentioned, adaptation is always contextual.

For molecular biologists, evolution is considered as progress, independent of the environment, in particular through the development of more and more complex regulatory mechanisms. The nature of variations determines the result, and a single variation is often sufficient: evolution proceeds by leaps. Ideas that evolution is the result of a complex accumulation of mutations, that each of them has a cost, and therefore that its retention comes from a trade-off between costs and benefits, are absent from the minds of molecular biologists.

Such a conception of evolution explains why molecular biologists emphasize the simplicity and generality of the basal mechanisms operating in organisms and, as we have seen, neglect the diversity of structures and functions generated by evolution.

The famous aphorism "What is true for *E. coli* is true for the elephant" was probably not Monod's, but the creation of an attendee at one of the lectures he gave, and an avatar of a sentence written long before by the Dutch biochemist Kluyver [19]. But Monod fully accepted it, and it faithfully reflected his thoughts.

Conclusion

Monod shared many convictions with other molecular biologists, but he pushed them further, and supported them with more vigor than most of his contemporaries. This is true for the three characteristics that we explored. *Chance and necessity* is famous for the virulent criticisms Monod addressed to all traditional metaphysical discourses on life. He not only tried to introduce the spirit of physics into the biological sciences, but through his work on allostery he also attempted to produce biological models similar to the scientific models used by physicists. And beyond his permanent acknowledgement of the importance of Darwinian theory, he tried to dovetail precisely functional and evolutionary explanations.

In the latter two cases, the efforts of Monod were not pursued by his contemporaries, who paid them little attention. In addition, Monod was convinced that natural selection was always a factor of progress, a conception that is outdated today. Nevertheless, Monod anticipated some of the most recent developments in biology: physical models are playing an increasing part in biology, and efforts to dovetail functional and evolutionary explanations have recently flourished.

On another point, however, the vision of Monod and early molecular biologists was very different from our current vision of the living world. Monod considered that all organisms obeyed simple principles of functioning that had been shaped by natural selection. This age of simplicity and universality is over. Present-day biologists prefer to emphasize the diversity of structures and functions created by long evolutionary history.

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Références :

[1] J. Monod, Le hasard et la nécessité. Essai sur la philosophie naturelle de la biologie moderne, Seuil, Paris, 1970.
[2] G.E. Allen, Rebel with two causes: Hans Driesch, in : O. Harman, M.R. Dietrich (Eds.), Rebels, mavericks and heretics in biology, Yale University Press, New Haven, 2008, pp. 37–64.
[3] H.F. Judson, The eighth day of Creation: makers of the revolution in biology, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1996, p. 545.
[4] M. Morange, A history of molecular biology, Harvard University Press, Cambridge, Mass., 1998.
[5] P. Debré, Jacques Monod, Flammarion, Paris, 1996, pp. 188–189.
[6] J. Monod, 1970, op. cit.
[7] J. Monod, F. Jacob, General conclusions: teleonomic mechanisms in cellular metabolism,

growth, and differentiation, Cold Spring Harbor Symp. Quant. Biol. 26 (1961) 389–401.
[8] J. Monod, J. Wyman, J.-P. Changeux, On the nature of allosteric transition: a plausible model, J. Mol. Biol. 12 (1965) 88–118.
[9] D.E. Koshland, G. Nemethy, D. Filmer, Comparison of experimental binding data and theoretical models in proteins containing subunits, Biochemistry 5 (1966) 365–385.
[10] M. Morange, A new life for allostery, J. Biosci. 37 (2012) 1–5.
[11] M. Morange, The scientific legacy of Jacques Monod, Res. Microbiol. 161 (2010) 77–81.
[12] M. Morange, Boris Ephrussi's continuing efforts to create a "genetics of differentiation", J. Biosci. 33 (2008) 21–25.
[13] J. Monod, Preface, in : K. Popper, La logique de la découverte scientifique, Payot, Paris, 1973, pp. 1–6.
[14] M. Cohn, In memoriam, in : A. Ullmann (Ed.), hommage à Jacques Monod : les origines de la biologie moléculaire, Études vivantes, Paris – Montréal, 1980, pp. 75–88.
[15] S.E. Luria, M. Delbrück, Mutations of bacteria from virus sensitivity to virus resistance, Genetics 28 (1943) 491–511.
[16] J. Monod, 1970, op. cit.
[17] S.J. Gould, R. Lewontin, The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme, Proc. Roy. Soc. London Series B 205 (1979) 581–598.
[18] E. Mayr, Cause and effect in biology, Science 134 (1961) 1501–1506.
[19] T.D. Brock, Milestones in microbiology, 1546–1940, ASM Press, Washington, D.C., 1999, pp. 247-261.