



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

Enzymatic cybernetics: An unpublished work by Jacques Monod



Cybernétique enzymatique. Un inédit de Jacques Monod

Jean Gayon

Institut d'histoire et de philosophie des sciences et des techniques (IHPST), UMR8590, Université Paris-1/CNRS/ENS, 6, rue du Four, 75006 Paris, France

ARTICLE INFO

Keywords:

Enzymatic adaptation
Cybernetics
Genetic determinism
Scientific method
Philosophy of biology

Mots clés :

Adaptation enzymatique
Cybernétique
Déterminisme génétique
Jacques Monod
Méthode scientifique
Philosophie de la biologie

ABSTRACT

In 1959, Jacques Monod wrote a manuscript entitled *Cybernétique enzymatique* [Enzymatic cybernetics]. Never published, this unpublished manuscript presents a synthesis of how Monod interpreted enzymatic adaptation just before the publication of the famous papers of the 1960s on the operon. In addition, Monod offers an example of a philosophy of biology immersed in scientific investigation. Monod's philosophical thoughts are classified into two categories, methodological and ontological. On the methodological side, Monod explicitly hints at his preferences regarding the scientific method in general: hypothetical-deductive method, and use of theoretical models. He also makes heuristic proposals regarding molecular biology: the need to analyse the phenomena in question at the level of individual cells, and the dual aspect of all biological explanation, functional and evolutionary. Ontological issues deal with the notions of information and genetic determinism, "cellular memory", the irrelevance of the notion of "living matter", and the usefulness of a cybernetic comprehension of molecular biology.

© 2015 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

RÉSUMÉ

En 1959, Jacques Monod a écrit un manuscrit intitulé *Cybernétique enzymatique*. Jamais publié, ce texte présente une synthèse des recherches sur l'adaptation enzymatique, qui précède immédiatement les fameuses publications des années 1960 sur l'opéron. Simultanément, Monod développe une philosophie de la biologie immergée dans l'investigation scientifique. Les réflexions de Monod sont classées en deux catégories, méthodologique et ontologique. De la première relèvent des réflexions générales sur la méthode scientifique (préférence pour la méthode hypothético-déductive et importance des modèles théoriques) et un ensemble de propositions de nature heuristique relativement à la biologie moléculaire (nécessité d'analyser les phénomènes au niveau des cellules individuelles, et dualité inévitable de toute explication biologique – fonctionnelle et évolutionnaire). Les réflexions de nature ontologique portent sur les notions d'information et de déterminisme génétique, sur la « mémoire cellulaire », l'inutilité de toute notion de « matière vivante », et l'utilité d'une compréhension cybernétique de la biologie moléculaire.

© 2015 Académie des sciences. Publié par Elsevier Masson SAS. Tous droits réservés.

Email address: jean.gayon@univ-paris1.fr.

<http://dx.doi.org/10.1016/j.crvi.2015.04.007>

1631-0691/© 2015 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

1. A unique manuscript

Jacques Monod (1910–1976) published two books under his own name. The first, entitled *Recherches sur la croissance des cultures bactériennes* [Researches on the growth of bacterial cultures] [1], was none other than his Doctor of Sciences thesis, defended in 1942. The second was a philosophical work published in 1970, a few years after the 1965 Nobel Prize: *Le hasard et la nécessité ; essai sur la philosophie naturelle de la biologie moderne* (English translation: *Chance and necessity: an essay on the natural philosophy of modern biology*) [2,3]. Between the publication of these two works, Monod composed a rather considerable manuscript in 1959, entitled *Enzymatic cybernetics* (Monod 1959). In terms of both style and purpose, this latter text is much closer to his thesis than is the 1973 work, aimed as it was at the general public. The manuscript in question is nevertheless of considerable scientific and philosophical interest.

This unpublished work is held at the Pasteur Institute archives. The manuscript is a typewritten document of 180 pages, double-spaced. Despite a few typographical errors, the document is written in a remarkably controlled, scientifically accurate and conceptually concise language. A number of authors are mentioned, but no specific bibliographic references are given. Numerous regions throughout the text have been left blank in order to accommodate equations, graphs, diagrams and tables, but no figures are given. A few simple genetic formulas, easily rendered using a typewriter, are provided in the last chapter. In the introduction, reference is made to a concluding chapter, more speculative in nature than the others, but absent from the manuscript we consulted. The book is therefore most likely unfinished.

This work is difficult to read for a non-specialist and is closely linked in terms of both expression and subject matter with the great scientific articles written by Monod in the late 1950s and early 1960s. Two aspects of this document would appear to require further emphasis. On the one hand, the manuscript is a kind of snapshot, which expresses with remarkable precision the state of the scientific question put forth by Monod. His analyses in this regard are the most advanced in his research at the time. Indeed, it is likely that the book was never published precisely because it was overtaken only a few months later by a series of major publications by Monod and his collaborators spanning the period from 1959 to 1963, during which time the concepts of the operon and allostery emerged. On the other hand, the range and scope of the scientific synthesis advanced in the 1959 manuscript breathes a kind of life into the paper absent from most if not all of the articles published during this period. While discussing certain technical developments, Monod shares with the reader some of his closely held opinions concerning his methodological choices, his conception of hypotheses and theories, and the challenges his hypotheses might present for biological theory. But nowhere are issues related to the philosophy of biology treated as topics to be dealt with in their own right, as is the case in *Chance and necessity*, whose subtitle, “Essay on the Natural Philosophy of Modern Biology” is quite explicit in this

regard. In *Enzymatic cybernetics*, reflection is occasionally given in the form of a few parsimonious lines highlighting certain scientific findings in the manner of a painter who accentuates contours using colour contrasts rather than a continuous line. *Enzymatic cybernetics* is a scientific synthesis that attempts on occasion to clarify some of its most fundamental underlying concepts.

Jacques Monod dictated the manuscript to Madeleine Brunerie in the space of three weeks, from 15 June to 7 July 1959, as attested by Brunerie's autobiography [4, p. 76]. Assuming the role of both secretary and lab technician, Brunerie worked alongside Jacques Monod from June 1954 to May 1976. *Cybernétique enzymatique* was to be co-signed by Melvin Cohn, but the two chapters that he was supposed to provide were ultimately written by Monod (Chapter Ia, “galactoside permease” and Section IVa, “Induction and cellular memory”).¹ Was it by chance that the manuscript was at once dictated and committed to paper with such great speed? Indeed, the book was based upon a series of lectures that were given by Monod at Harvard University (*Durham Conferences*) in the fall of 1958, under the title “The natural history of the bacterial enzyme systems”.

In this study, we first situate Jacques Monod's *Enzymatic cybernetics* within its proper scientific context. We then present various theses from the philosophy of biology such as they are found dispersed throughout the manuscript.

2. *Enzymatic cybernetics*: a scientific synthesis

The focus of this work's analysis is identical to that which recruited the better part of Jacques Monod's energies, from his doctoral thesis in 1942 to the contributions that eventually earned him the Nobel Prize in Physiology and Medicine in 1965 alongside André Lwoff and François Jacob. Monod proposes a synthesis of all available knowledge regarding the phenomenon of enzymatic adaptation, that is to say of enzyme induced biosynthesis in bacteria, with the example of the β -galactosidase from *Escherichia coli* taken as the experimental reference system. But from the outset the author outlines two of the manuscript's more general ambitions. He explains that his intention is to further elucidate the enzymatic mechanisms of induction and repression by demonstrating how they are ultimately subject to a form of “genetic determinism”. This objective is itself subsumed under a more general formula.

Indeed, according to Monod, the text is devoted to the topic of “enzymatic cybernetics”. In a first draft of the

¹ The manuscript contains seven sections each with its own numbering: “Introduction. Retrospectives and Prospectives” (20 pp.); “Chapter I. β -galactosidase and galactoside permease in *E. coli*” (17 pp.); “Chapter Ia. Galactoside permease” (16 pp. numbered 1 to 14, because there are three pages numbered 5 (5, 5', 5'')); “Chapter III. Kinetics and dynamics” (2 + 32 pp.); “Chapter IVa. Induction and cellular memory” (19 pp.); “Chapter V. Repression and feedback inhibition” (2 + 31 pp.); “Chapter VI. The genetic determinism of enzymatic adaptation” (41 pp.). We note the absence of chapter II. The “a” (Chapter Ia and chapter IVa) probably designate sections to be undertaken by Melvin Cohn. Regardless, and in the words of Madeleine Brunerie, these chapters amount to the “first draft” produced by Monod. Because the pages of the manuscript are numbered with respect to the chapters, all references to that manuscript mention the title of the chapter quoted. All translations are ours.

manuscript, the term “cellular cybernetics” was used; however, the adjective “cellular” was later crossed out and replaced with “enzymatic” [4, p. 6]. Regardless, this is the only occurrence of the word “cybernetics” throughout the whole of the manuscript, with the exception of its use in the title. Fearing its eventual journalistic resonances, Monod apologizes for the use of this term, even though he feels it is to be preferred over others:

“Moreover, we hope to demonstrate that genetic determinism is not limited to the structure of macromolecules synthesized by a cell, but that the mechanisms of induction and repression are themselves directly subject to a form of genetic determinism. The subject of the essays contained herein cannot therefore be limited to enzymatic adaptation as such and might best be described in terms of enzymatic cybernetics, if only this term, which has become fashionable, did not invoke for the reader the alarming journalistic resonances [sic] [4, Introduction, p. 6]”.

Enzymatic cybernetics occupies a pivotal place in the scientific work of Jacques Monod. Here are a few indications to this effect.

If we were to try and position this work relative to the author’s scientific output, we might locate it immediately before the “years of wonders” – to paraphrase a formula applied to Albert Einstein – during which Monod and his associates elaborated upon the concepts of messenger RNA, allostery, the operon, as well as those of operator and promoter sequences. These findings were concentrated in large part between the years 1959–1961, later converging and culminating in 1963 [5–12] (the majority of Monod’s collected scientific articles can be found in [13]). The 1959 manuscript therefore appeared just before this exceptional scientific harvest as it were. What then, might we justifiably inquire, did Monod seek to express in *Enzymatic cybernetics* that was of such importance? In 1959, Monod believed that he and other specialists of enzymatic adaptation had reached a plateau in their journey of discovery. Without going into the details behind the well-established propositions that Monod lists emphatically throughout the book, and not without a certain triumphalism, we might mention a few of them.

Monod determined in 1959 that he had established, among other things: that the metabolism of lactose required, in addition to β -galactosidase (enzyme degrading galactose), a permease (that is to say, a permeating protein enabling penetration of the substrate, galactose, into the bacterial cell) [4, Chap Ia.]; that these two proteins were synthesized *de novo* in the presence of the substrate [4, Chapter III]; that the phenomenon of the feedback inhibition of gene expression needs to be carefully dissociated from that of the repression of enzyme synthesis [4, Chapter V]; that this synthesis can only be explained at the genetic level [4 Chapter VI]; that this required a distinction between two categories of genes from a molecular point of view, informant genes (later called “structural genes” because they carry information determining the structure of proteins) and “regulatory genes” (which control the synthesis of repressors

[4, Chapter VI]); that the phenomenon of repression was probably more fundamental than that of induction, and that it constituted the “primary mechanism” controlling enzymatic synthesis [4, Introduction, p. 4–5, and Chapter V]; that this control was strictly dependent on a form of “genetic determinism” [4, Chapter VI]. This list only provides an overview of the established propositions that succeed each other across the manuscript’s 180 pages. Clearly, this is no small affair. In point of fact, during the summer of 1959, Monod was of the opinion that the molecular mechanisms of enzyme adaptation (the physical nature of the repressor, as well as the nature of its interactions with the inducing substrate and genes) in all of their intricacies would not soon be discovered. The following excerpt betrays this conviction:

[...] we are almost entirely ignorant of the molecular mechanisms behind the interaction between the formation centre of enzymes, inducer and repressor, as well as the nature of the endogenous repressors. There is hope that these problems will be dealt with 10 to 15 years from now in future essays [4, Introduction, p. 18].

But in point of fact, it only took two years before the majority of these puzzles were more or less solved. This is why a text that at first blush appeared to be at the forefront of knowledge was never ultimately published. In the articles published between 1959 and 1963, and for which we provided a list above, one will note the recurrence of terms, such as “mechanisms” and “genetic control” in the very titles themselves.

Another indication of this text’s pivotal place in Monod’s corpus is given by the author’s collaborations before and after the manuscript’s release. With a few rare exceptions, Monod essentially collaborated with biochemists. But beginning in 1959, we see him repeatedly publishing alongside François Jacob, with whom he signs the majority of articles published between 1959 and 1963. Their collaboration coincided with both the emergence of genetic methods in the treatment of enzymatic adaptation, and with some overlap in their respective explanations for the lysogenic cycle. The 1959 manuscript is driven by the idea that genetics holds the answers to many of the problems confronting them and it concludes with the initial results obtained by Arthur Pardee and François Jacob in 1959, the latter being only sparsely referenced throughout *Enzymatic cybernetics* [5].

The figures given by Monod in his articles before and after 1959 offer a third indication as to *Enzymatic cybernetics* role as a kind of symbolic turning point. Prior to 1959, the figures given by Monod are almost exclusively graphs representing reaction kinetics. These graphs are associated with chemical equations (mass equations). After 1959, the biochemical equations and graphs are still there, but the text is gradually taken over by genetic maps, formulas expressing genotypes, and abstract diagrams variously representing the hypothetical mechanisms behind gene regulation, intermolecular interactions, hypotheses relative to allostery, often deeply inspired by Jean-Pierre Changeux (for whom Monod acted as Doctoral advisor), most notably in regard to allosteric mechanisms [14–16].

3. A philosophy of biology immersed in scientific conjecture

As previously stated, the manuscript *Enzymatic cybernetics* is not written as an essay on the philosophy of biology or, to cite the subtitle of the book *Chance and necessity*, as an “Essay on the natural philosophy of modern biology” [2,3]. One can, however, uncover a set of moderately developed theses, outlining the contours of Jacques Monod’s fundamental conceptions of biology as a theoretical science. These theories are not presented in such a way as to conform to the kind of autonomous conceptual agenda that prevails in *Chance and necessity*. In contrast, these theories frame and circumscribe a dense scientific exposé, further explicating Monod’s fundamental theoretical commitments. The classification of these theories as proposed herein has no basis in the architecture of the manuscript. Our efforts at interpretation will not, however, go beyond this classification. We have remained resolutely descriptive relative to the content of Monod’s proposals.

Enzymatic cybernetics contains two varieties of theses relative to the philosophy of biology. The first category is methodological in thrust and the second deals with ontology, that is to say a conception of the entities and abstract propositions which regiment the vision of the biological world offered by Monod in his manuscript. Neither the term ontology nor methodology is present in the text.

3.1. Methodological options

Monod’s methodological theses easily fall into two categories: those related to the scientific method in general and those related to biology in particular.

Monod defends the scientific method that is his own. His remarks at this juncture could be understood without special reference to either the biological sciences or the specific questions dealt with by the author. But it is clear that it is in relation to his own research that these questions are formulated. Monod’s method is adumbrated in a small paragraph that concludes the introductory chapter, and resonates throughout the entire manuscript:

“It is impossible to logically or meaningfully discuss experimental data without the use of theoretical models. When discussing the relations between enzymatic formation systems, inductor, repressor and genes, models of this kind can sometimes appear abstract, simplistic and unreal. This is unproblematic provided such models lead to the formulation of hypotheses. We will attempt, however, in the following chapters, to limit theoretical discussions to the models directly related with the data under scrutiny, reserving more general speculations and attempts at synthesis for a concluding chapter [4, Chap. I, p. 20]”.

These lines when appropriately viewed in relation to Monod’s various other reflections on “theoretical models”, dispersed as they are throughout the text, illustrate the following:

- (1) The hypothetical-deductive method is considered by Monod to be the fundamental scientific method. This is a characteristic and almost obsessive feature of the approach displayed in the work’s details as well as in all of his scientific articles. This method consists in freely advancing hypotheses and in testing them – either directly or more often by way of their consequences – and in drawing on enigmas that themselves generate further hypotheses and theses still and so on *ad infinitum*. We can better understand this commitment if we compare it with other styles of experimental research widely practiced in modern times. There is little place in Monod’s conception of research for purely descriptive and inductive phases of research, neither do exploratory experiments (the ‘experiments to see what happens’ dear to Claude Bernard) appeal to him, nor is he partial toward a form of research that begins with a conjecture before progressing toward specific experiments;
- (2) Monod is also an adept of “theoretical models”. Traditionally, in both the philosophy of science and in scientific practice, models are understood to be stylized, simplified, abstract representations that fulfil a heuristic function. Monod shares this point of view and adheres to a pragmatic and instrumental view of theories;
- (3) This pragmatism is, however, tempered by the distinction he makes between testable hypotheses and conjectures. Monod allows for both, but carefully distinguishes between them in his introductory remarks and throughout the manuscript. Although the speculative concluding chapter mentioned by Monod is not available, the manuscript develops numerous conjectures, which are even referred to as such. These are sometimes generalizations of hypotheses (e.g., the idea that regulatory mechanisms are fundamentally retro-inhibitors rather than inducers), or attempts at extending certain models to other research domains (e.g., incursions into development or cancer research). In arguing for “conjectures” and not only “theoretical models”, Monod thereby affirms the legitimacy of theory, over and above “models”. Theory is not limited to “models”.

Other methodological remarks found in *Enzymatic cybernetics* do not originate from a general philosophy of the science framework, but are rather heuristic principles specific to the life sciences. We can identify essentially three heuristic principles, all of which are presented in the context of discussions on the biological sciences.

The first of these principles underscores the limitations peculiar to the traditional tools of biochemistry – reaction kinetics and chemical analysis – in explaining metabolic phenomena. According to Monod, we must move beyond studies of populations of cells and metabolites, and beyond structural descriptions, in order to focus on “mechanisms”. This is one of the manuscript’s leitmotifs, and it is particularly significant in light of the fact that Monod was able to draw as much upon his 1942 thesis on diauxie during the 1960s as upon the kinetics of enzymatic reactions. Now the 1959 manuscript coincides with a

period during which Monod recognizes the inadequacy of this method, and begins to argue that we must combine kinetics with hypotheses about molecular mechanisms, that is to say hypotheses about the individual behaviour of molecules or of larger molecular systems, without limiting ourselves to mass behaviour:

“The natural tendency of the experimenters who have studied basic cellular processes has naturally led them to seek the interpretation of these phenomena in the fundamental laws of classical physics and chemistry which are statistical laws and ultimately reducible to the gas laws. But with each passing day it becomes increasingly clear that the elementary phenomena of cell physiology are not reducible to statistical laws, but rather to mechanisms whose construction and complex and precise circuits are not unlike those of a machine [4, Chap. I, p. 17]”.

The same perspective is adopted at the end of Chapter IVa, on “cellular memory”. Monod once again adduces a methodological reflection, all the more significant given that it is formulated by a biochemist who had devoted most of his earlier work to mass action kinetics:

“To conclude, let us once again emphasize the extreme importance of the problem of the homogeneity of the response to an agent or any condition in a cell population. As we have seen, certain conditions can promote and cause a heterogeneous response in a genetically homogeneous population. The observed kinetics of the entire population can therefore no longer reflect cellular events. Consequently, the analysis of cells or of clones is indispensable. This notion, common among geneticists, is less widely held among biochemists and physiologists. But advances in cellular physiology will increasingly require *the direct analysis of phenomena at the level of individual cells* [4, Chap. IV a, p. 19. Emphasis added]”.

Let us try and fully grasp the author’s intentions as expressed in the above quote. By claiming that “cellular events” must be taken into account and that phenomena at the level of individual cells must be analysed directly, Monod does not mean that we must directly observe *one and only one* molecular event, or even *a single* cellular event isolated from all others. This possibility is not excluded, but neither is it necessary (“Analysis of cells or of clones is therefore indispensable”; emphasis added). The idea here is to distinguish a statistical method that deals with populations as such (cell populations, metabolite populations), from methods whose purpose is to describe individual phenomena, despite the fact that these phenomena are more often than not discovered by identifying properties endemic to homogeneous groups (e.g., the genetic determinism of cells of the same clone, or properties – physicochemical, serological, etc. – of a purified metabolite). This is somewhat reminiscent of the distinction made historian of science by Alistair C. Crombie, who delineates six major styles of scientific research and demonstration, and then classifies these methods into two groups: methods that reveal “individual

regularities”, and those concerned with “populations of objects” [17, p. 83–87].

The second heuristic principle adduced by Monod in *Enzymatic cybernetics* amounts to the claim that it is first and foremost genetics that allows and will allow for the discovery and most especially the explanation of the molecular mechanisms at work in cell biology. Regarding bacteria, the field of genetics is indeed working on massively homogeneous clones whose properties are invariants right down to the last mutation. It is at this level, according to Monod, that we must try and uncover true biological laws that are not the laws of mass action but rather conjectures about the molecular mechanisms at work in the specific properties of cells, or more precisely, conjectures about the invariants that regiment the operation of the machines that are cells. This principle will only be fully formulated in these terms in *Chance and necessity* given that *Enzymatic cybernetics* is more cautious in advancing these ideas. The author intervenes throughout the memoir whenever a formula is to be presented and indicates that it is ultimately at the genetic level that the question of the synthesis and control of enzymatic adaptation can find a solution. The introduction to Chapter VI, entitled “The genetic determinism of enzymatic adaptation” and entirely dedicated to elaborating upon the progress made on this issue, exemplifies Monod’s mind set in 1959 relative to this subject:

“The discussions of the two previous chapters have shown that any hypothesis about the mechanism of induction and repression involves an interpretation of the genetic and functional difference between inducible and constitutive systems. We have already mentioned the involvement of specific mutations that convert a typical inductive system into a constitutive system. Genetic analysis of these mutations, their interactions with other elements of the genome and the study of their biochemical expression should eventually lead to an interpretation of enzymatic adaptation, whether repressive or inductive. This is the subject of this chapter [4, Chap. VI, p. 1]”.

The latter heuristic principle is a corollary to the former. It is discretely but firmly stated at the outset of the work. By focusing on genetics as key to the explanation of the basic mechanisms of cellular metabolism, Monod foregrounds evolution as the ultimate level of biological explanation, in contrast with current mechanisms, that is, more immediate mechanisms currently operating in the space and time of the phenomenon under experimental investigation. The author lets a little phrase slip, through which he expresses this idea poignantly. Having called the reader’s attention to the idea that genetic and molecular analysis place the concept of information centre stage, Monod writes: “Consequently, it is clear that both the problem of the immediate and evolutionary origin of protein structures are laid bare” [4, Introduction, p. 9]. This proposal is not unlike the distinction Ernst Mayr made between “proximate causes” and “ultimate causes”. We know that Mayr published his celebrated article “Cause and effect in biology” in the journal *Science* in 1961

[18]. But he had already presented the article orally, and we now know that he inherited many of the ideas expressed therein from a long tradition of thought specific to ornithologists [19]. It is not entirely implausible that Monod, who would later work toward and preface the publication in French of a book by Mayr entitled *Populations, species and evolution* [20], had the opportunity to hear Mayr's thoughts on this topic during the Durham lectures at Harvard in 1958, from which the manuscript *Enzymatic cybernetics* was born. This point would need to be documented. Regardless, in 1959 Monod had a clear vision of the hierarchy of biological causes to which Mayr would later accustom us. Although this point might at first appear trivial, it was a matter of some importance for the French biologist, and especially laboratory biologists, of the time. In *Enzymatic cybernetics*, Monod is keenly aware of the fact that the genetic level is the locus for the articulation between “immediate causes” and “evolutionary causes”, as the following phrases, which immediately follow the above-cited quotation, illustrate:

“The genetic determinism of protein structure is therefore thought to be at work in a very immediate and precise manner once the enzymatic mechanism of adaptation is considered. Modern theories have assigned genes the function of reproducing and transferring information relative to the sequence of amino acids in the peptide chains of proteins [4, Introduction, p. 9]”.

We cannot resist juxtaposing the aforementioned prescriptions with those used by Mayr in “Cause and effect in biology”:

“We can use the language of information theory to attempt still another characterization of these two fields of biology.² The functional biologist deals with all aspects of decoding the programmed information contained in the DNA code of the fertilized zygote. The evolutionary biologist, on the other hand, is interested in the history of these codes of information and in the laws that control the changes of these codes from generation to generation [18: 1503]”.

3.2. Ontology

Monod's reflections on issues of methodology carry him to the threshold of ontological commitments. In what follows we will catalogue these commitments in order from the most specific to the most general.

We might first take into account Monod's analysis and qualification of enzymes in terms of “Maxwell's demons”. Widely adopted and developed in *Chance and necessity*, this idea comes at the conclusion of Chapter Ia, dedicated to the permease involved in the lactose system. At the conclusion of this chapter, Monod extends a remark he makes concerning this particular protein, which determines the

passage of lactose through the cell membrane of the bacteria, to all enzymes. As galactoside permease selects an external substrate and plays an important role in the relationship between the external environment and the intracellular medium, so too are enzymes generally “the choice elements, Maxwell's demons orienting and distributing metabolites and the chemical potential toward syntheses, growth and cell multiplication [4, Chap. Ia, p. 14]”. This sentence, written somewhat offhandedly, and inserted between other phrases dealing specifically with permeation factors, is typical of the kind of conjectural insights Monod allows himself on occasion, and for which he sometimes but not always provides further elaboration. By extending the notion of “Maxwell's demons” to enzymes, the author stresses the primacy of mechanisms over mass actions thereby pointing toward the molecular effectors that confer on the physical chemistry of life its special trajectory. It should be recalled that, in the manuscript's original French title *Cybernétique enzymatique*, the word ‘enzyme’ follows the first word of a merely two-word title.

Of much greater significance is Monod's commitment to “genetic determinism”. The entire work converges toward the sixth chapter, entitled “The genetic determinism of enzymatic adaptation”. In this chapter, Monod reproduces much of the substance of the famous Pardee–Jacob–Monod article published that same year in the first volume of the *Journal of Molecular Biology* [5]. In this article and in Chapter VI of *Enzymatic cybernetics*, an important distinction between “informing genes” (*gènes informateurs*, later renamed “structural genes”) and “regulatory genes” is introduced. It is within this context that the author claims that vital chemical syntheses are “governed” by genes only as a kind of last resort, and that genes alone are able to provide an invariant basis for cellular mechanisms:

“The analysis of the galactoside permease system therefore indicates that the synthesis of an inducible enzyme is governed by two specific genes, the first of which, provisionally labelled here as informant gene, contains structural information about the protein molecule, and the second, that is, the regulatory gene, controls the expression of the first via a cytoplasmic repressor [4, Chap. VI, p. 24]”.

On the last page of the manuscript, these findings are again taken into consideration when explicit mention is made of the concept of “genetic determinism”:

“At this point, we would like to briefly clarify the concepts that emerge from the genetic study of adaptive systems.

The most important, and we believe, the most currently well-established of these concepts, is the existence of a double genetic determinism in the synthesis of many proteins. This determinism results from the intervention of two distinct genes. The first gene establishes the structure of the synthesized molecule, while the second gene, or regulatory gene, controls, that is to say allows for or prevents the expression of the first [4, Chap. VI, p. 41]”.

² That is, “functional biology” (or the biology of proximate causes) and “evolutionary biology” (or the biology of ultimate causes).

In the 1959 manuscript, Monod does not offer any general thoughts on genetic determinism. Nevertheless, he clearly uses this notion in support of the idea that, *vis-à-vis* the very phenomenon he set out to research, namely, enzymatic adaptation, both the structure of the effector protein (galactosidase) and the mechanism controlling its synthesis (repressor) are determined at the genetic level. The last lines of Chapter V directly pave the way for the succeeding chapter's treatment of "the genetic determinism of enzymatic adaptation" and hint at the above-mentioned philosophical thesis (ontological commitment) via a precise scientific conjecture, thereby offering us a perfect illustration of Monod's theoretical style:

"... these observations further emphasize the critical importance of the study of constitutive mutations. Such a study necessarily involves an analysis of the genetic determinism at work in these mutations and the relationship between the determinants that govern constitutivity and those that govern the structure of the synthesized protein. This will be the subject of the following Chapter [4, Chap. V, p. 31]."

The third ontological thesis concerns "cellular memory". It is introduced in chapter IVa ("Induction and cellular memory"), which was originally supposed to have been written by Melvin Cohn, but was later taken up by Monod himself on the basis of a collaborative piece. Even though the term "Lamarckism" is never used here, as indeed the term is nowhere mentioned in Monod's scientific writings, or so it would seem, Lamarckism is nevertheless clearly the focus of the author's inquiry at this juncture. The language employed here is quite explicit. Monod inquires as to "how induction [enzyme] can leave a permanent trace in both the induced cells and their progeny [4, Chap. IVa, p. 2]". The author speaks of "durable modifications" that induction via a substrate could confer on progeny after multiple generations [4]. Following a somewhat virtuoso demonstration, Monod establishes that such modifications exist, but that:

- (1) they only last for a limited number of generations (among the cases examined, he cites a "memory" effect experimentally demonstrated across more than 250 generations [4, Chap. IVa, p. 8];
- (2) durable modifications in enzymatic adaptation to galactose are due to the persistence of permease molecules and galactosidase in the cell lines;
- (3) enzymatic adaptation's "memory" gradually disappears due to the progressive dilution of these molecules, as cells divide;
- (4) durable modifications leave no room for ideas of self-replicating molecular systems because, in point of fact, the phenomenon under scrutiny amounts to autocatalysis broadly conceived, whereby the product of galactosidase retroacts on permease – which in turn continues to facilitate the penetration of lactose –, even at doses that fail to provoke a reaction in a bacterial cell with no memory of lactose.

The chapter that deals with the problem of "cellular memory" is particularly challenging and takes on an

importance all its own in light of current studies on epigenetic effects in bacteria. We cannot enter into any further details regarding Monod's rather dense and compact argument. Suffice it to say that the issue of "durable modifications" is crucial to the history of the French school of molecular biology. It is our contention that this school was driven by a desire, unparalleled elsewhere in the world, to examine Lamarckism at the most basic level of physiologic analysis possible, and at the highest level of experimental rigor available at the time. No doubt the French school was not alone in its fascination with Lamarckism; however, the French school did pursue this question to its utmost limit, and it did so with one notable distinction that bears mentioning. For with the exception of a few rather provocative statements made by André Lwoff at the end of his life, the three 1965 Nobel laureates in Physiology and Medicine (Jacob, Lwoff, Monod) carefully avoided using the term "Lamarckism" in their scientific writings. The Chapter in *Enzymatic Cybernetics* devoted to "Cellular Memory" is symptomatic of this. In it, Monod elaborates on the presence of the rather troubling phenomena of induction, which leave a lasting mark on cell progeny, and he endeavours to invalidate the neo-Lamarckian explanations that could be advanced at the time, without using terms, such as "Lamarckism", "neo-Lamarckism" or "inheritance of acquired characteristics". It is not that he entirely rejected open debate on Lamarckism but rather, when he did engage in this debate, and he did so avidly during the 1950s, it was within a strictly political context.

The fourth ontological thesis of the 1959 manuscript deals with nothing less than "life" itself. This thesis is expressed in Chapter III, entitled "Kinetics and dynamics", where Monod summarizes the achievements of the kinetic approach to enzymatic reactions, while at the same time pleading for a massive influx of hypotheses on molecular mechanisms. For the first time, Monod's confidence openly extends its reach beyond the discussion of the experimental data at hand. We have only to direct our attention to the title of the chapter, and we note that the words "kinetic" and "dynamic" are not on the same level: "kinetic" refers to the chemical method in which Monod excelled, whereas "dynamic" refers to a general conception of life that Monod rejects. Let us turn to the author's own words on the matter in the following, and unusually lengthy, 'philosophical' development:

"The traditional image of life as the unstable, trembling and constantly recreated flame of a candle is deeply anchored within each one of us, whether or not we happen to be biologists. And indeed, this image describes life and its constant and uncertain struggle against entropic tendencies such as they appear to us at the macroscopic level. Instinctively and implicitly, we tend to project onto the microscopic, molecular world our experience and our descriptions of the macroscopic world. Consequently, we speak of "living matter" and of the "living molecule". The concept of a dynamic state compelled us to represent "living molecules" themselves as unstable units that could only be maintained at the cost of some continuous effort and creative act.

And, in this molecular dynamicity, we might hope to glimpse the very movement if not the secret of life itself. Clearly, however, the very idea of “living matter” or of a “living molecule” does not correspond to any reality. For only cells are truly alive, as opposed to mere molecules, and the image of the candle flame does not apply at the molecular level. (...) All of the advances in modern molecular biology demonstrate [...] that the essential features of living things are related to the accuracy, complexity and stability of their macromolecules [4, Chap. III, pp. 31–32].”

The above citation leaves little room for commentary. The “dynamic” of life images marshalled by Monod are evocative of Henri Bergson. But more importantly, an entire tradition of biochemical neo-vitalism is here rejected outright. Claude Debru has commented admirably on the images generated by this train of thought in *L'esprit des protéines* [*The spirit of proteins*] [21]. He argues that crystallized forms of macromolecules (including proteins) were considered to be nothing more than amorphous skeletons of what the same molecules are within the living cell.

The fifth and final thesis of biological ontology that can be identified in the 1959 manuscript is the most inclusive of all. We shall conclude with this point, given that it leads us back to the title of the manuscript itself. This thesis is not expressed using explicit abstract statements, but by the very lexicon that traverses the entire work, especially the introduction and chapters V and VI. We have already mentioned that Jacques Monod used the word “cybernetics” only once throughout the text, and not without specifying that this term was indeed appropriate to the topic of the book: “The subject of the essays contained herein cannot therefore be limited to enzymatic adaptation as such and might best be described in terms of enzymatic cybernetics, if only this term, which has become fashionable, did not invoke for the reader the alarming journalistic resonances [4, Introduction, p. 6]”. Nowhere, however, in the manuscript is this term defined by Monod, nowhere is it commented on further; nowhere is it referenced. Perhaps Monod would have done so in the concluding chapter, to which he refers repeatedly throughout the manuscript (Introduction and Chap. VI), but we do not have this chapter. In the absence of any relevant argument, we nevertheless have a lexicon at our disposal, which builds up from beginning to end until such time as it saturates the final chapter's scientific exposé on the “genetic determinism of enzymatic adaptation”. Here are these terms, all of which were abundantly made use of and more often than not justified with care; “information”, “chemical decision”, “self-induction”, “feedback inhibition”, “repression” (defined as a special form of inhibition), “regulation”, “control”, and “governing” (the governing of syntheses and processes by genes). These words speak for themselves. Monod has indeed written an enzymatic

Cybernetics, not just a synthetic work on enzymatic adaptation.

Acknowledgements

This article is a revised version of a study previously published in French in C. Debru, M. Morange & F. Worms (Eds.), *Une nouvelle connaissance du vivant. François Jacob, André Lwoff et Jacques Monod*, Paris, Éditions rue d'Ulm – Presses de l'École normale supérieure, 2012, pp. 27–44. I thank Éditions rue d'Ulm for authorizing this adaptation. I am greatly indebted to Gabi Lipede for his translation.

References

- [1] J. Monod, *Recherches sur la croissance des cultures bactériennes*, Hermann, Paris, 1942 (2nd ed. 1959).
- [2] J. Monod, *Le hasard et la nécessité ; essai sur la philosophie naturelle de la biologie moderne*, Éditions du Seuil, Paris, 1970.
- [3] J. Monod, *Chance and necessity; an essay on the natural philosophy of modern biology*, translated from the French by Austryn Wainhouse, Knopf, New York, 1971.
- [4] J. Monod, *Cybernétique enzymatique*, unpublished typewritten document deposited at the Pasteur Institute archives, Paris.
- [5] A.B. Pardee, F. Jacob, J. Monod, The genetic control and cytoplasmic expression of β -galactosidase by *E. coli*, *J. Mol. Biol.* 1 (1959) 165–178.
- [6] F. Jacob, D. Perrin, C. Sanchez, J. Monod, L'opéron : groupe de gènes à expression coordonnée par un opérateur, *C. R. Acad. Sci. Paris* 250 (1960) 1727–1729.
- [7] M. Riley, A.B. Pardee, F. Jacob, J. Monod, On the expression of a structural gene, *J. Mol. Biol.* 2 (1960) 216–225.
- [8] F. Jacob, J. Monod, Genetic regulatory mechanisms in the synthesis of proteins, *J. Mol. Biol.* 3 (1961) 318–356.
- [9] F. Jacob, J. Monod, On the regulation of gene activity, *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 26, Long Island Biological Association, Cold Spring Harbor, N.Y., 1961, pp. 193–211.
- [10] F. Jacob, J. Monod, General conclusions: teleonomic mechanisms in cellular metabolism, growth, and differentiation, *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 26, Long Island Biological Association, Cold Spring Harbor, N.Y., 1961, pp. 389–401.
- [11] F. Jacob, J. Monod, Genetic repression, allosteric inhibition, and cellular differentiation, in: M. Locke (Ed.), *Cytodifferentiation and Macromolecular Synthesis*, Academic Press, New York, 1963, pp. 30–64.
- [12] J. Monod, J.-P. Changeux, F. Jacob, Allosteric proteins and cellular control systems, *J. Mol. Biol.* 6 (1963) 306–329.
- [13] A. Lwoff, A. Ullmann, *Selected Papers in Molecular Biology* by Jacques Monod, Academic Press, New York, San Francisco and London, 1978.
- [14] J.-P. Changeux, The feedback control mechanism of biosynthetic ι -threonine deaminase by ι -isoleucine, *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 26, Long Island Biological Association, Cold Spring Harbor, N.Y., 1961, pp. 313–318.
- [15] J.-P. Changeux, Allosteric interactions on biosynthetic ι -threonine deaminase from *E. coli* K12, *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 28, Long Island Biological Association, Cold Spring Harbor, N.Y., 1963, pp. 497–504.
- [16] J.-P. Changeux, Sur les propriétés allostériques de la ι -thréonine désaminase d'*Escherichia coli* K12, [Thèse présentée à la faculté des sciences de l'université de Paris pour obtenir le grade de docteur ès sciences naturelles, Paris], 1964.
- [17] A.C. Crombie, *Styles of scientific thinking in the European tradition: the history of argumentation and explanation especially in the mathematical and biomedical sciences and arts*, Duckworth, London, 1994.
- [18] E. Mayr, Cause and effect in biology, *Science* 134 (1961) 1501–1506.
- [19] J. Beatty, The proximate/ultimate distinction in the multiple careers of Ernst Mayr, *Biol. Philos.* 9 (1994) 333–356.
- [20] E. Mayr, *Populations, espèces et évolution*, Hermann, Paris, 1974.
- [21] C. Debru, *L'esprit des protéines. Histoire et philosophie biochimiques*, Hermann, Paris, 1983.