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

Jacques Monod: Fifty years after – Foreword

Jacques Monod : 50 ans après – Avant-propos

Fifty years ago, François Jacob, André Lwoff, and Jacques Monod received the Nobel Prize in physiology or medicine "for their discoveries concerning the genetic control of enzyme and virus synthesis". This distinction was awarded in recognition of an exceptional series of discoveries and theoretical achievements: existence, induction and genetics of lysogeny, notions and evidence of repressor, regulatory genes, messenger RNA, operon, operator and promoter sequences, and allostery. These discoveries involved many more people than the three laureates (especially Élie Wollman, François Gros, Jean-Pierre Changeux); they were also the occasion of a remarkable cooperation and interaction between them and other key figures in the history of molecular biology (especially, Max Perutz, Francis Crick, Sydney Brenner). Jacques Monod (1910–1976) played a central role in most of these achievements, except for lysogeny). This issue offers a portrait of Monod as a theorist whose contributions powerfully shaped the intellectual image of molecular biology.

The first outcome of this collective enquiry was to clearly identify Monod's main scientific contributions. As noted by Maxime Schwartz, Monod, not unlike Louis Pasteur, was a fervent supporter of basic science. But, in contrast to Pasteur, at no point was his research dictated by the desire to solve a practical problem of any kind. Most of his scientific work was devoted to a single problem: the description and explanation of enzymatic adaptation in bacteria. Henri Buc, however, calls attention to the fact that this experimental system led him to two major discoveries that stand on different levels. The first breakthrough was to understand the respective roles of the inducing substrate and of the specific genes that determine and control the production of the enzyme (beta-galactosidase). The second contribution went far beyond enzymatic adaptation, and consisted in the discovery, or rather the proposal, of the allosteric model. Both contributions had a high theoretical potential. The first discovery was the result of an impressive collaboration between a number of Pasteurians and culminated in the notion of the operon, which itself involved the distinction between structural and regulator genes. In 2011, François Jacob made the following commentary on the occasion of the 50th anniversary of the discovery of the operon, i.e., very first example of how genes are turned on and off: "we quickly recognized that the operon-repressor system could be combined *ad infinitum* to produce circuits of increasing complexity, adapting to the demands of the cell. Thus did we discover a 'mechanism fundamental to all living beings from their very beginnings, and that would persist as long as they exist...' [1]" [2]. This commemorative declaration can be further nuanced: when the lactose operon was discovered, it had a tremendous potential from a theoretical point of view [3]; however, in practice, its experimental applicability was limited to a short list of operons in bacteria. The case was different for allostery, which was immediately applied to a number of cases, namely hemoglobin, the repressor, L-threonine deaminase, aspartate transcarbamylase, and many other enzymes. Henri Buc observes that Monod immediately conceived of allostery in a much more general terms as "a product of evolution acting in all kingdoms of life". Allostery offered almost immediately a way of explaining and uniting big classes of biological phenomena, and therefore represented a genuine theory [4]. As noted recently by Stuart Edelstein, "the concept of allostery captured important features and united four distinct streams of research: (1) feed-back-inhibited enzymes, (2) bacterial genetic repressors, (3) hemoglobin, and (4) membrane receptors." [5] It is no coincidence that Monod chose to comment on allostery in his Nobel lecture [6], and that he qualified its discovery as "the second secret of life" [7].

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The second and most distinctive benefit of this issue is to offer a characterization of Monod's style of research, and indeed all the authors have contributed to this result. This style can be characterized in three different but complementary ways.

(1) As a theorist, Monod was haunted by an ideal, normative view of what a good scientific theory should be. A good theory had to be simple, as general as possible, and heuristically fertile (Buc). Heuristic power is difficult to characterize, because it is mainly an a posteriori property that may result from different possible effects of a theory, e.g., its applicability to various classes of phenomena, allostery being an obvious example; its exemplarity, i.e. its ability to generate additional theories, which nevertheless retain something, but not necessarily everything, of the initial theoretical model, as this was certainly the case for the first model of genetic regulation, the operon; and lastly, its ability, however speculative in nature, to generate possible alternatives, providing a sort of landmark that stimulates scientific imagination and experimentation, as has indeed been the case with respect to allostery in the past fifty years.

Simplicity and generality are more precise epistemic values. Monod was haunted by them. Philippe Morange argues that this has something to do with Monod's admiration for physics. Although Monod was definitely not trained as a physicist, and was not really a specialist in physical chemistry, he was nevertheless motivated to imitate the way in which physicists think and work: he sought general laws (as evidenced in his early work on the growth of bacterial populations); he thought that the study of simple models was the best way to solve big issues, in biology as well as in physics; and he came to emphasize genetics over all else in biology because he believed that genetics is the biological discipline that most closely resembles physics.

(2) Beyond his visceral attachment to simple and general theories, Monod had a relatively articulated reflection on scientific methodology. All of the authors in this issue pay heed to what could be rightly called "Monod's philosophy of science", visible here and there in a number of articles, manuscripts, talks, and most especially in *Chance and Necessity* [8–9], which is commented on by most of the authors, as well as in the unpublished manuscript *Cybernétique enzymatique* [10], analyzed by Jean Gayon. Monod had a non-inductivist conception of science: he was convinced that the scientific reasoning is basically hypothetico-deductive, and this is why he was so enthusiastic about Popper when *The Logic of Scientific Discovery* was translated into French, with a preface by him [11]. We would like to quote an excerpt from this preface: "Applied to contemporary biology, [Poppers's analyses] appear to be as much perceptive and close to the theoretico-empirical reality as they were for physics in 1920" [11, p. 5]. Monod's keen interest in Popper's analyses is in keeping with his various declarations in favor of models, especially theoretical models.

Monod's epistemology was not, however, inviolable and unvarying. Laurent Loison shows that he changed his mind significantly regarding the subject of determinism in biology. In his original work on biochemical kinetics, which extended over a period of at least two decades, he adhered to statistical determinism, with explicit reference to physics. It is only in the late 1950s that he began to support mechanistic explanations as applied to individual molecules. Another subject on which Monod's thinking tended to vary was chance. Francesca Merlin convincingly shows that, in *Chance and Necessity*, Monod adopted at least three different concepts of chance. Although these concepts do not really contradict each other, they were freely used by Monod in different theoretical contexts and it is unclear whether Monod was fully aware of the plurality of concepts he advanced in relation to chance.

(3) Monod's style of scientific thinking was also related to his disciplinary profile. His original domain of expertise was not that of a structural biochemist, or even a specialist of metabolism, but rather that of a biometrician working on the kinetics of growth of bacterial cells (Loison, Morange, Gayon). Neither was he not a chemical physicist, a discipline in which he was something of an "amateur" (Buc). Remarkably, however, his major achievements consisted in hypothetical and fruitful conjectures about the changing configurations of proteins. Another facet of Monod's disciplinary background was reflected in his interest in genetics, which he discovered at the start of his PhD while accompanying Boris Ephrussi to Thomas Hunt Morgan's lab at Caltech, in 1936. Although Ephrussi declared: "I brought him to California to study genetics. He made my life miserable", and although genetics is absent from Monod's PhD, this early contact with genetics probably left a long-lasting impression on his mind.

The third contribution of this issue is to clarify Monod's philosophy of biology. This expression is certainly not inappropriate, given that it appears in the subtitle of *Chance and Necessity*, both in French and in English: *An essay on the natural philosophy of modern biology (Essai sur la philosophie naturelle de la biologie moderne)* [7–8]. In contrast to both François Jacob, who thought that "life" was an outdated concept in modern biology, and most of the standard literature in the philosophy of biology that has developed since the beginning of the 1970s, Monod was not loath to speculate on "life". Evelyn Fox Keller recalls and discusses at length of the three distinctive properties that Monod attributed to life: teleonomy, autonomous morphogenesis, and invariant reproduction. She shows how, in reality, Monod privileged just one of these three properties, invariant reproduction. Autonomous morphogenesis was for him a mechanistic and deterministic outcome that was not distinctively biological. As for teleonomy, it was anchored in the particular structure of proteins, especially allosteric enzymes. Therefore, everything in living beings for Monod was rooted in DNA, whose sequence dictates the polypeptidic structure of proteins.

Laurent Loison, who concentrates on Monod's ultimate "molecular determinism", prefers to insist on another trilogy: rigidity, stability, and specificity. This aspect of Monod's thinking has been underestimated because of the complications introduced by allostery. But Monod's conviction was that the cell's molecular machinery exhibited three distinctive properties: rigidity of molecular operations (and more specifically of the genetic program), intrinsic stability of organic macromolecules (even if they can shift from one configuration to another), and specificity of molecular interactions. These theses can be best identified in Monod's harsh criticisms of the classical "dynamical view" of proteins. Loison recalls a passage of the Nobel lecture where Monod admitted that he had been led, during the 1950s, to "seriously question" the traditional dogma of the "dynamic state" among biochemists. Monod's 1959 manuscript also includes impressive attacks against the "dynamical view of life" (Gayon).

The fourth contribution of this issue is provided by Soraya de Chadarevian and Maxime Schwartz, who analyze Monod's institutional involvement. Schwartz insists that Monod's research agenda was never dictated by technical or practical problems. But both Chadarevian and Schwartz recall how involved Monod has been in institutional matters. As early as 1956, he played an active role in the Caen colloquium, which led to a voluntaristic research policy promoting, among other things, molecular biology. Then, from 1960 to 1970, Monod played a decisive role in the creation of the Institute for Molecular Biology at the Pasteur Institute. Finally, as director of the Pasteur Institute (1971–1976), he both guaranteed the recognition of basic research (especially in molecular biology) in that Institute, and reorganized the Institute so as to make it a more independent structure via the development of its "production sector". Monod was therefore faithful in a sense to the spirit of Pasteur: much like Pasteur, but in his own way, Monod's professional life brought together and united the two aspects of basic and applied science.

All of the aspects of Monod's biography finally converge on what Soraya de Chadarevian characterizes as a "discipline builder": he was a master in his field, he was celebrated for his teaching (something that did not interest Crick, for example), he was deeply involved in institutional politics, and he worked hard to provide a philosophical foundation for the "new biology".

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