The "Genetic Program": Behind the Genesis of an Influential Metaphor

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ABSTRACT The metaphor of the "genetic program," indicating the genome as a set of instructions required to build a phenotype, has been very influential in biology despite various criticisms over the years. This metaphor, first published in 1961, is thought to have been invented independently in two different articles, one by Ernst Mayr and the other by François Jacob and Jacques Monod. Here, after a detailed analysis of what both parties meant by "genetic program," I show, using unpublished archives, the strong resemblance between the ideas of Mayr and Monod and suggest that their idea of genetic program probably shares a common origin. I explore the possibility that the two men met before 1961 and also exchanged their ideas through common friends and colleagues in the field of molecular biology. Based on unpublished correspondence of Jacob and Monod, I highlight the important events that influenced the preparation of their influential paper, which introduced the concept of the genetic program. Finally, I suggest that the genetic program metaphor may have preceded both papers and that it was probably used informally before 1961.

KEYWORDS program; genetic program; developmental program; Ernst Mayr; François Jacob; Jacques Monod; teleonomy

AFTER World War II, many physicists turned toward biology and brought Descartes' metaphor of "animal machines" closer to reality, with the difference that the machines were now electric computers run by programs. For many decades, the word "program" had meant a planned series of events, carrying that usage in common language; it then acquired another meaning, indicating a series of coded instructions to control the operation of a computer (*New Oxford American Dictionary*) and a related meaning in biology in the form of the "genetic program." Unlike other metaphors invented at the same time, such as "messenger RNA" and "genetic code," the genetic program metaphor continues to trigger debate about its appropriateness and hence its usefulness.

Precisely what is meant by "genetic program" and whether it is a good (or even useful) metaphor actually constitute a long-running controversy. Keller (2000) argued that the cell could also be seen as the program and DNA as the data (but not all the data). As a "developmental program," the metaphor, it was pointed out, misses the temporality aspects (Wilkins 1986), the influence of physical properties and mechanical forces during development (Goodwin 1985; Noble 2006), the role of symbiosis in defining individuality (Gilbert and Epel 2008), and the inescapable role of the environment (Oyama 2000). This ongoing debate (and any other reference to the metaphor) almost always quotes the same two articles for what is believed to be the genesis of the metaphor in 1961: one by molecular biologists François Jacob and Jacques Monod (Jacob and Monod 1961) and the other by evolutionary biologist Ernst Mayr (Mayr 1961). Interestingly, neither article acknowledges the other. Since the two articles are different in style and took root in two distinct fields, the independent birth of the genetic program metaphor in these two articles has never been questioned. However, an analysis of both articles and the later writings of the three authors about the genetic program suggests that Jacob, Monod, and Mayr either shared the same influences or that they met and discussed the idea before 1961. The story of the genetic program also reveals strong connections that existed between physicists, geneticists, molecular biologists, and evolutionary biologists at that time.

The Well-Known Beginnings of the Metaphor

The article by Mayr (1961) is a short philosophical analysis entitled, "Cause and Effect in Biology," published in the American Association for the Advancement of Science

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(AAAS) journal *Science* in November 1961. In contrast, Jacob and Monod's article is a very long review reporting the work that eventually led to their Nobel Prize in 1965; their paper was published on June 10, 1961, in the *Journal of Molecular Biology*. Taken as the reference point for the birth of the genetic program metaphor, these two articles have the interesting commonality that the words "genetic program" are written verbatim nowhere in either.

Teleology is to Mayr one of the three fundamental aspects of causality; usually associated with "goal-seeking behavior," it raises the problem of purpose. According to Mayr, events such as growth, development, reproduction, and behavior are "seemingly purposive" and appear to be in contradiction with a mechanistic interpretation of nature, where everything is causally explained in terms of "physical and chemical phenomena." Rejecting the mechanistic interpretation, vitalists explained goal-directed processes such as development in terms of "vital force." This debate about purpose has its origin in Aristotelian philosophy (Falcon 2014). Aristotle identified four types of causes, as illustrated by the making of a bronze statue: a material cause, what the statue is made of; a formal cause, what the shape of the statue is; an efficient cause, the source of the transformation of the bronze into a statue, namely, the artisan; and a final cause, the end to which the statue is made. Teleology refers to this last cause. We can ask, "Why was a statue made?" or "What is its purpose?" and answer, "For the pleasure of watching it." For the statue, the maker is the source of the purpose, but who is the maker of an organic being? For Mayr, the maker is natural selection, which acts by selecting the best route for constructing organic beings. This perspective changes the question of "Why?" into "How come?" Mayr proposed that a solution to the problem of purpose can be found using the "language of information."

An individual who—to use the language of the computer—has been "programmed" can

> act purposefully. ... The completely individualistic and yet also species-specific DNA code of every zygote (fertilized egg cell), which controls the development of the central and peripheral nervous systems, of the sense organs, of the hormones, of the physiology and morphology, is the *program* for the behavior computer of this individual. Natural selection does its best to favor the production of codes guaranteeing behavior that increases fitness. ... The purposive action of an individual, insofar as it is based on the properties of its genetic code, therefore is no more or less purposive than the actions of a computer that has been programmed to respond appropriately to various inputs" [Mayr 1961, pp. 1503–1504].

For Mayr, the value of the program metaphor is to make the use of purpose in biology a legitimate one. Notice that he uses the two words "program" and "code" interchangeably. At that time, the modern meaning of "genetic code" (translation from codons to amino acids) was not yet established and was a synonym for "protein synthesis" (Kay 2000). Mayr's program is a species-specific developmental program. The use of "program" triggers a shift from teleology to what Mayr termed "teleonomy" ("apparent purposeness") and to "teleonomic" (a "descriptive term for all end-directed systems not committed to Aristotelian teleology"). On this basis, he proposed two main kinds of causes for "systems operating in the basis of a program." He took the example of bird migration, where "physiological conditions" and environmental effects are "proximate causes," while the "lack of food during winter" and the "thousands of generations of natural selection" shaping the "genetic disposition of the bird" are the "ultimate causes." Rephrased in terms of genetic program, proximate causes relate to the expression of the programmed information, and ultimate causes relate to the history, the writing by evolution, of the genetic program from generation to generation. This allowed Mayr to introduce a second distinction: decoding the programmed information is the work of "functional biologists," and understanding its history is the work of the "evolutionary biologists." Therefore, two of Mayr's most important distinctions—functional/evolutionary biology and proximate/ultimate causes—are consequences that derive from the genetic program metaphor. Interestingly, the genetic program served molecular biology's triumph in developmental biology, whereas the functional/evolutionary biologist distinction was used by evolutionary biologists to criticize their molecularist colleagues, arguing that they were not doing true biology but "chemical reactions and physical models" [see Milam (2010) for a detailed review of the so-called molecular wars].

The article by Jacob and Monod (1961) is entitled, "Genetic Regulatory Mechanisms in the Synthesis of Proteins"; it summarizes years of research on the lactose and lysogenic systems in *Escherichia coli* with the purpose of showing that genes are "both necessary and sufficient to define the structure of a protein" and that mechanisms of control of protein expression "operate at the genetic level." The article is filled with informational metaphors, many of which were created by Jacob and Monod: "operator," "operon," "messenger RNA," and "program." The last two, messenger RNA and program (in the sense of genetic program), are the first published occurrences in the scientific literature. After detailing "experimentally established conclusions," which "apply strictly to the bacterial systems," Jacob and Monod devoted a short and final paragraph to speculation. They suggested that their model of the control of protein synthesis by regulator genes could apply to embryology and cancer by explaining how cells bearing the same genome have different phenotypes and behaviors; their model, they concluded, is based on the idea of the program:

> According to the strictly structural concept, the genome is considered as a mosaic of independent molecular blueprints for the building of individual cellular constituents. In the execution of these plans, however, co-ordination is evidently of absolute survival value. The discovery of regulator and operator genes, and of repressive regulation of the activity of structural genes, reveals that the genome contains not only a series of blue-prints, but a co-ordinated program of protein synthesis and the means to control its execution [Jacob and Monod 1961, p. 354].

This short paragraph gives less detail about their "program" than Mayr does about his, but it is still rich in meaning. While Mayr's metaphor lay at the basis of his thesis, Jacob and Monod's "program" is not less ambitious but remains a strictly speculative way to analyze the major experimental results presented in the rest of the paper. Jacob and Monod's model introduced three different things: (1) "a series of blue-prints," (2) "a co-ordinated program of protein synthesis," and (3) "the means of controlling its execution." All are included in the genome. Notice that the genetic program (the "co-ordinated program") is not the whole genome but only a portion of it, and it is therefore an organizational component for the rest of the genome. Thus, it is not a blueprint for proteins, meaning that it is different from the transcribed DNA sequences for structural proteins. Finally, it is different from the "means of controlling its execution" (the other cellular components). These distinctions are crucial because they show that Jacob and Monod's program is not what will be called "the data" by Keller (2000) and other critics of the genetic program metaphor. The embryology context in which they introduce the metaphor suggests that it can be thought of as a developmental program but not as the sufficient and necessary element for the development of an organism or the life of a cell; the "series of blue-prints" and the "means of controlling its execution" are important as well. Nevertheless, Jacob and Monod's program, like Mayr's, is clearly a genetic program because it resides in the genome, and in essence, they both consider it a model for the control of development. In contrast to Mayr, however, Jacob and Monod's article remains silent about teleology.

Bringing Together the Two Program Metaphors

After 1961, both Mayr and Jacob contributed to the success of the metaphor by promoting it extensively in their writings. What they both meant by "program" converged to a single concept, helped by their later discussions and encounters. However, Monod used the word rarely. Mayr seemed the most enthusiastic about the concept. In *The Growth of Biological Thought* (Mayr 1982), Mayr wrote that "the genetic program provides for an absolute difference between organisms and inanimate matter" (Mayr 1982, p. 56) and that the "genetic program" is the "most significant" "aspect of inheritance" (Mayr 1982, p. 629). Using the same words as Jacob and Monod (1961), he wrote that the "genetic program" is the "genome," which obviously consists of "DNA molecules" and "serves as a blueprint, as a set of instructions," made possible by "the code [in the modern sense], with the help of which the program is translated into the individual organisms" (Mayr 1982, pp. 826–828). Also, "it endows the organisms with the capacity for teleonomic processes" (Mayr 1982, p. 56) because the "genetic program has provided a mechanistic explanation of one class of teleological phenomena" and that "all the processes of individual development ... are guided by a program, and they depend on the existence of some endpoint goal" (Mayr 1982, pp. 48–49). Mayr's enthusiasm is perceptible when he states that "all manifestations of development and life are controlled by genetic programs" (Mayr 1982, p. 106). He adds that this implies that "all parts of biology are branches of genetics," a claim that is "not altogether as absurd it may seem" because "the genetic program in some way or another is involved in all biological activities (even where open programs control a certain action)." Altogether this demonstrates "the central and integrating role of genetics in biological thought" (Mayr 1982, p. 630). He also mentions precursors of the idea of the genetic program, such as August Weismann, who came "very close to proposing that development is controlled by a genetic program" (Mayr 1982, p. 702), and he also agrees with Max Delbrück that "Aristotle's *eidos* (even though considered immaterial because invisible) was conceptually virtually identical with the ontogenetic program of the developmental physiologist. Buffon's 'moule intérieure' was a similar ordering device" (Mayr 1982, p. 56).

In 1978, Mayr was invited to Paris by Jacob to give a series of lectures on the theory of evolution. The lectures were transformed into a book published in French (Mayr 1981). A section of the book is dedicated to the problem of teleology and another to the "signification of the word program":

> The term "final cause" goes back to Aristotle and means, from his own formulation, "in the purpose of what" something exists or takes place. For example, the adult individual is the purpose of why ontogenesis takes place. ... The researchers working on teleology ended up discovering suitable concepts used in cybernetics and the information theory and adapted them well. The result was the development of a new language where appeared the words like "information", "program" and "retroactions". This language allows avoiding of traditional objections made against the teleological language [Mayr 1981, pp. 110–113].[1]

For Mayr, informational metaphors such as program are the solution to the problem of purpose in biology, allowing conceptual progress in scientific thinking. He stated that the word "program" becomes the "key word" to his definition of teleonomy (Mayr 1981, p. 117), which he differentiates again from teleology:

> Such clear cut separation of teleonomy, which has a physiochemical basis which can be analyzed, from teleology, which deals more broadly with the over-all harmony of the organic world, is most useful because these two entirely different phenomena have so often been confused with each other [Mayr 1981, p. 48].

For Mayr, the breakthrough in scientific thinking in the shift from teleology to telonomy was made possible by joining Darwin's theory of natural selection with the concepts of cybernetics and information theory. Jacob wrote in the Preface of Mayr's book that the theory of evolution "gives a causal explanation of the living world." They both agreed that the "program" carried that idea.

[1]All translations from the French are by the author.

Jacob also made an intensive use of the genetic program metaphor. In the *Logic of Life* (Jacob 1970; Jacob 1973 for an American translation), he went much beyond the original "program" of the 1961 paper and seemed to converge toward Mayr's view:

> In the genetic programme, therefore, is written the result of all past reproductions, the collection of successes, since all traces of failures have disappeared. The genetic message, the programme of the present-day organism, therefore, resembles a text without an author, that a proof-reader has been correcting for more than two billion years, continually improving, refining and completing it, gradually eliminating all imperfections. What is copied and transmitted today to ensure the stability of the species is this text, ceaselessly modified by time. Time, in this case, means the number of consecutive copies of the message, the number of successive generations leading from a remote ancestor to our present-day bacterial cell [Jacob 1973, p. 287].

As was the case for Mayr, the program is clearly an historical account of past effects of natural selection toward a better adaptation of the organisms bearing it. Interestingly, the word "programme" in the French edition (Jacob 1970) is translated for an American publisher in British English and written "programme" rather than "program." In U.S. English, the "program" belongs to computers and the "programme" is a schedule, an agenda. The distinction is not trivial; it has been suggested (Morange 2002, pp. 59–60) that the origin of the genetic program metaphor may rather lie in this second meaning of "program" and that Monod and Jacob may have been less influenced by computer science. Indeed, when Jacob and Monod (1961) mentioned a "co-ordinated program of protein synthesis," it could be understood as the original meaning of "program" ("program" in U.S. English, "programme" in British English, and "programme" in French): an organized series of events, like a conference program, a research program. The genetic program would be a schedule of necessary gene expression steps for development or for physiological responses; this would be similar to a program for launching a rocket, where a series of steps are necessary to reach the final goal, the takeoff (Morange 2002, p. 60). Regarding the problem of goal-ended processes, Jacob (1973) wrote

> In any case, it is reproduction which functions as a principal operator of the living world. On the one hand, it is a goal for each organism. On the other hand, it orients the history without a goal of organisms. For a long time the biologist has been consorting with teleology as with a woman without whom he can't live, but with whom he doesn't want to be seen in public. To this hidden relationship, the concept of program gives a legal status [Jacob 1973, p. 17].

This is a very similar statement to that of Mayr (1961, p. 1503), who stated that using "the language of computers," speaking of an individual organism that has been "programmed" makes the question of "purpose" "legitimate." Jacob gave an even more detailed picture of the genetic program in a French interview aired on televison in 1979. He explained that "modern biology" has brought us "the concept of genetic program" and added that

> [t]he 46 chromosomes [of a human embryo] contain the program to make a child. That is, it doesn't contain the full description like the homunculus [referring to earlier preformationist theories]; it contains the program, that is, the instructions necessary for producing on one hand, the molecules, essential to make the adult, and on the other hand the means of producing them in time and space. . . . How it is planned for which molecule will express itself in time and space, in which conditions, how the cells will differentiate from each other, of this we have no idea for the moment, simply no idea. In other words, what is the computer language, the language spoken by this program. . . . [T]his we don't know at all [Jacob 1979, 00:20:00–00:21:30].

The tone seems less speculative than that of Jacob and Monod (1961). We see Jacob (1979) converging with Mayr's enthusiasm by stating that the idea of the genetic program is the accomplishment of modern biology. He also converges with Mayr on the fact that the analogy came from computer language (but was that how he thought of it originally?). Nevertheless, he distances himself from a hard version of genetic determinism. What follows in the interview is truly worth quoting:

> THE JOURNALIST: By simplifying the phenomenon, we could affirm that we are totally programmed from birth, that our entire life is written in our genes, in short we would only have a minute space of liberty.
>
> JACOB: No, of course not, what is written in advance is that when a man and a woman make a child, it is the child of a human and not the child of a dog or an elephant, and conversely, when two flies make a child, it is not the child of a sycamore or a diplodocus. That [part] is programmed, that is the general structure of the body. But, of course, the entire individual is the result of an interaction between his genes and the medium, genes give borders, borders on the size of an individual and say whether the individual will have blue eyes, but it doesn't go further. You must not believe and I really don't want to say that intellectual qualities or mental qualities are programmed. There has been, a few months ago, the return of a very old polemic between nature and nurture [in French *l'inné et l'acquis*], a completely unreasonable polemic where it has been attempted to see in the intellectual performance of an individual, on both the racial and individual aspect, what is the proportion which is nurture and which is nature. This is a way to tackle the problem which is completely stupid. It is like asking for the part of nature and the part of nurture in Romeo's love for Juliet [Jacob 1979, 00:22:00–00:23:44].

Jacob's statement regarding the program is clear. He acknowledges that in the program lies the essence of the species (but not all the details of each individual). He answers harsh criticisms that will be made regarding his concept of genetic program (although on other occasions he was not always so careful). Despite his enthusiasm regarding the importance of the metaphor, Jacob had already warned readers of *Logique du vivant* (Jacob 1970) about the limits of the metaphor; here we see that he is strongly opposed to a generalization of the metaphor to intellectual capabilities, and his analogy with Romeo's love for Juliet captures the limitations of the idea.

Monod seemed less enthusiastic about the metaphor and rarely used it (Maurel and Miquel 2000). In his major essay, "Chance and Necessity," Monod (1970) used the word "program" to designate a plan of action made for a machine (or an alien) that would have to decide on a given number of properties of living beings on Earth. However, Monod wrote that "the organism is a machine which builds itself" (Monod 1970, p. 60) and that "the cell is a machine" (Monod 1970, p. 125). After giving details about biochemical processes relative to proteins, he spoke of their "complexity and efficiency in the accomplishment of a program written in advance" (Monod 1970, p. 72) and of "reproductive invariance" as the capacity to reproduce "at each cellular generation the text written under the form of DNA, which allows the invariance of the species" (Monod 1970, p. 119). These views, however, suggest a strong similarity with both Mayr and Jacob.

Like Mayr, Monod was preoccupied by teleology and purpose. In Le Hasard et la Nécessité, he wrote that living beings are "endowed with a project" that is "both in their structure and which they accomplish through their performances" (Monod 1970, p. 22), and like Mayr, he made the same distinction between teleology and teleonomy (purpose from conscious decision *vs.* purpose derived from natural selection's purposeless actions) by stating that living beings belong to the second concept. This project carried by each living being is what he calls the "invariant reproduction" (Monod 1970, p. 27), which is what Mayr and Jacob called "the program." In fact, Monod had been concerned by the problem of purpose in biology since his beginnings in biology. For him, goal-directed explanations in biology had to be replaced by natural explanations, much like what had happened in physics with Galileo and Newton. This ambition was probably one of Monod's motivations to turn toward biology (Morange 2008, 2010). Monod's personal notebook reveals that he was intensely interested in philosophical problems. In November 1955, he wrote that there are three eras for "scientific philosophy"; the first one is the "animist or teleological era," which is represented by "Aristotle, etc. [his words]"; the second, ongoing era is the one where "phenomena are explained by their final causes"; and the third era, the "empirical and rational," is the one where "objective laws make operational rules" (Monod 1955). In the same notebook, later in the same month, he realized the fundamental split between Aristotle's physics and modern physics as a result of Galileo:

> The discovery by Galileo of the inertia principle can be considered as the essential rupture between modern physics and Aristotelian physics: in the description of the motion of celestial bod[ies], inertia replaces the will [Monod 1955, p. 32].

The problem of teleology was clearly important in biology. Norbert Wiener, an American mathematician, had co-authored a paper in 1943 entitled, "Behavior, Purpose, and Teleology," in which he suggested that "the method of studying organisms and machines was similar" (Rosenblueth *et al.* 1943). Regarding Wiener's essential work, Kay (2000, p. 85) wrote that he "transformed Schrödinger's statistical mechanical arguments into an information discourse encompassing all self-regulating systems." The strength of Wiener's ideas lay in his interaction with biologists, such as J. B. S Haldane:

> Partly through his ongoing dialogue with Haldane, an enthusiastic convert to cybernetics, Wiener prophesied a cybernetics of heredity by invoking the then-dominant view of the primacy of proteins. . . . As in all transmissions of messages, such a protein-based genetic transmission could be ultimately explained by information theory [Kay 2000, p. 86].

In 1948, Haldane wrote to Wiener that "a mutation seems to be a bit of noise which gets incorporated into a message"; he added: "If I could see heredity in terms of message and noise, I could get somewhere" (Kay 2000, p. 87). Wiener's interest in cybernetics reached France, where an article entitled, "Cybernétique et les fonctions nerveuses," was published in the newspaper *Le Monde*. The article stated that "[c]ybernetics is a new science and has the goal of studying the control and communication in machines, living beings and communities" (Lemaire 1950). It is impossible to know whether Monod read this article, but in 1959, he prepared a manuscript in French entitled, *Cybernétique enzymatique* [Enzymatical Cybernetics].

Cybernétique enzymatique

Monod dictated this one-hundred-and-eighty-page book to his secretary, Madeleine Brunerie, between June 15 and July 7, 1959 (Brunerie 2009), but it was never published. The content of the book is essentially similar to what was written by Jacob and Monod (1961). Monod wanted to "show that genetic determinism does not limit itself to the structure of macromolecules synthesized by a cell, but that the induction and repression mechanisms are themselves submitted to a genetic determinism" (Monod 1959a, p. 1). Although there is no reference to the "genetic program" or "program" in the manuscript, Monod mentions the possibility of extending his model of genetic control to development: "the induction and repression studied in microorganisms furnish therefore the principle or models of action or specific interaction which could one day explain some aspects of cellular differentiation" (Monod 1959a, p. 11). And concerns about teleology in biological systems are also in the manuscript, meaning that the ideas linked to the genetic program were already there. In fact, Monod had the idea to write this book after giving the prestigious Dunham Lectures at Harvard in October 1958 (Monod 1959b) on "the natural history of bacterial enzymes systems." An article in the *New England Journal of Medicine* summarized the content of the lecture:

> According to Dr. Monod, the enzyme inducer acts upon a pre-existing center, presumably a gene, which releases "information" concerning the amino acid sequential pattern

> of the enzyme structure. This "information" is utilized by the specific enzyme-forming center, which may be either a cytoplasmic template of the gene itself. . . . His parting remark is that the philosophical goal of a biologist is to prove that "living organisms are completely absurd creatures which know only how to obey blind laws" [Gross 1959].

Monod counted on the lectures to make his point about the purposeless behavior of living beings. The importance of absurdity, the meaninglessness of the world, in Monod's philosophy can be linked to French existentialism, which had a strong influence on him (Carroll 2013). Overwhelmed with work, he never finished the book (Monod 1960a), and he started to write with Jacob the synthesis article (Jacob and Monod 1961) that introduced the idea of "the program" in 1961. Originally, the article was supposed to be part of the book (Monod 1960a), meaning that "the program" would have been introduced in a teleological context, and this would have made the convergence with Mayr's view even more striking. Gayon (2013) has shown that in *Cybernétique enzymatique*, Monod understood that genetics is the key level to explain metabolism, and he clearly considered evolution as the ultimate level of biological explanation. This led him to introduce the same distinction of causes as Mayr (1961) and to write that "[i]t is clear that the problem arises of the immediate origin and of the evolutionary origin of the structure of proteins" (Monod 1959a, p. 9). Therefore, Mayr and Monod were both concerned with teleology, they made the same distinction between two types of causes, and both tried to solve this by a model of genetic control, except that Monod did not call it a "genetic program" yet. Gayon (2013) also noticed the very surprising convergence on the matter of teleology (teleonomy) and the problem of causes but did not mention the third convergence regarding the "genetic program":

> It is not improbable that Monod who will work towards the publication in French of the book *Population*, *Species*, *and Evolution* [a book written by Mayr in English and published in 1970], and who wrote its Preface, had the occasion to hear Mayr on this subject when he gave at Harvard, in 1958, the "Dunham Lectures" which are at the origin of the manuscript of *Cybernétique enzymatique*. This point should be documented [Gayon 2013, p. 38].[2]

If Monod and Mayr had met before the publication of their articles in 1961 and exchanged ideas on their philosophical interest regarding biology, then the double birth of the genetic program metaphor in 1961 probably was not the coincidence it appears to be.

Possible Encounters

Monod's archives at the Institut Pasteur are extremely detailed and thorough. Madeleine Brunerie, Monod's assistant, spent much of her life after Monod's death assembling a complete record of Monod's exchanges with the world, personal notes, unpublished manuscripts, and laboratory books. When she only had the answer to a letter Monod had received, she contacted the sender and asked for a copy in order to add it to the archives. A full inventory of every item in the archives is now computerized to facilitate research. Jacob's archives are also well documented, but to a lesser extent than Monod's. Despite an extensive search within the archives of the Institut Pasteur and an online search in the archives of Mayr, I did not find a single piece of evidence of an encounter between Monod or Jacob and Mayr. Of course, it is impossible to affirm that something is surely not in the archives considering its immensity, but Madeleine Brunerie's considerable work make it possible to come close to it. Nevertheless, this does not rule out the possibility of an undocumented encounter. Multiple ties appear to have existed between Monod and Mayr. A number of their common friends could have either triggered an encounter between them or communicated one's thoughts to the other. Another alternative is that the genetic program metaphor and its meaning is older: it may have been used informally by several biologists without realizing its originality until Mayr, Jacob, and Monod published it for the first time without considering themselves as the creators.

Mayr's 1961 article in *Science* was not the first time he mentioned the problem of "cause and effect in biology." His article was adapted from a lecture he presented on February 1, 1961, at the Hayden Colloquium on "Cause and Effect" organized at the Massachusetts Institute of Technology. He was the only biologist to speak during the colloquium but probably not the only one in the audience. The content of the lectures was published in a book edited by Lerner (1965) that is based on a combination of written contributions from the authors and an audio recording of the sessions (as acknowledged by Lerner in the Introduction). When the text is based on a published article (even if it was published after the conference), Lerner mentions it. For Mayr's lecture, there is no mention of an already published article. In a quick reading, Mayr's text in Lerner (1965) may appear strictly identical to his *Science* article. But something essential has changed: multiple occurrences of the word "code" in the Mayr (1961) article are changed to "program" in Lerner (1965). If this text is a true transcription of what Mayr said during the lecture, then the first occurrence of the genetic program metaphor occurs when Mayr suggests that "old arguments of biological philosophy can be stated far more precisely in terms of these genetic programs" (Lerner 1965, p. 36); this would make the genetic program metaphor a few months younger than June 1961 (date of publication of Jacob and Monod's article) and make Mayr its first user in a scientific communication. The first time that Mayr used "genetic program" (and not its plural form) occurred when he spoke of "the purposive action of an individual, as far as it is based on the properties of its genetic program therefore, is no more nor less purposive than the actions of a computer that has been programmed"

[2]Translated from the French by the author.

(Lerner 1965, p. 40). The sentence is exactly the same as in Mayr (1961) except that "genetic code" has become "genetic program." It is troubling that almost nothing except these very words were changed between the two texts. Multiple questions remain on this edited version of Mayr's lecture. Was Mayr contacted by Lerner (after 1961) to get a written version of his speech in order to publish it? Mayr could have taken his *Science* article and exchanged "code" for "program" not least because by 1965 it was starting to take its current meaning as a result of the code having been cracked. This would imply that Mayr's original metaphor would have been "genetic code" and that to differentiate it from the codon translation table, he had used a synonym, "program." It also could be because Monod and Jacob had used it, and he wanted to make a link. To my knowledge (from contacting the AAAS and searching online in Mayr's Harvard archives), there are no records on the publication process of either text.

Mayr had been working at Harvard since 1953, and in 1961, he was a professor there as well as director of the Museum of Comparative Zoology. Since 1956, he had been part of the same faculty as James D. Watson. The two men knew each other quite well since the end of the 1940s, given that Mayr had a property at Cold Spring Harbor, close to the laboratory where Watson had completed his Ph.D. with Salvador Luria (Mayr 2002). Mayr was involved in Watson being recruited to Harvard (Mayr 2002). "Watson's crowd" (as Mayr calls it) was physically very close to Mayr's office in the Museum of Comparative Zoology, and interactions between people in the two buildings occurred often during the 1960s, especially at lunch (Henri Buc, personal communication, 2014). It is not impossible that Mayr developed his knowledge about molecular biology and his idea of the genetic program through interactions with "Watson's crowd" or other molecular biologists. Spending time at Cold Spring Harbor led Mayr to become interested in molecular biology (Mayr 2002). Thus, it is likely that he continued to attend conferences on the subject at Harvard. Moreover, James Watson had multiple interactions with Jacob and Monod (Jacob 1987), while in 1960 François Gros moved from Monod's laboratory to Watson's laboratory to study messenger RNA (Morange 1994, Kay 2000), similar work to that mentioned in Jacob and Monod (1961).

Between 1935 and 1936, Monod spent a year in Thomas H. Morgan's laboratory, where he discovered *Drosophila* genetics. In his own words, this was a "revelation" (Monod 1954). By 1958, he had become a very well-established researcher at the Pasteur Institute, which led to the invitation to give the prestigious Dunham Lectures at Harvard. It was hardly his first stay on the East Coast, however. By 1958, he had been there at least 10 times (Monod 1958a), including in 1955 and in 1957, when he spoke at Harvard (Monod 1958a); these were multiple occasions when he could have met with Mayr. During his visit for the Dunham Lectures, he planned a tour of the country to visit institutions where he had friends and former colleagues (Figure 1). He arrived in New York on October 15, gave the lectures at Harvard during the week of October 20, and flew back to Paris from San Francisco on November the 25, 1958. In a month and a half, he had given at least eight talks across the country. For the Harvard lecture, entitled, "The Natural History of Bacterial Enzymes Systems," Monod had prepared notes that resemble the comments in Jacob and Monod (1961). In those notes, he stated

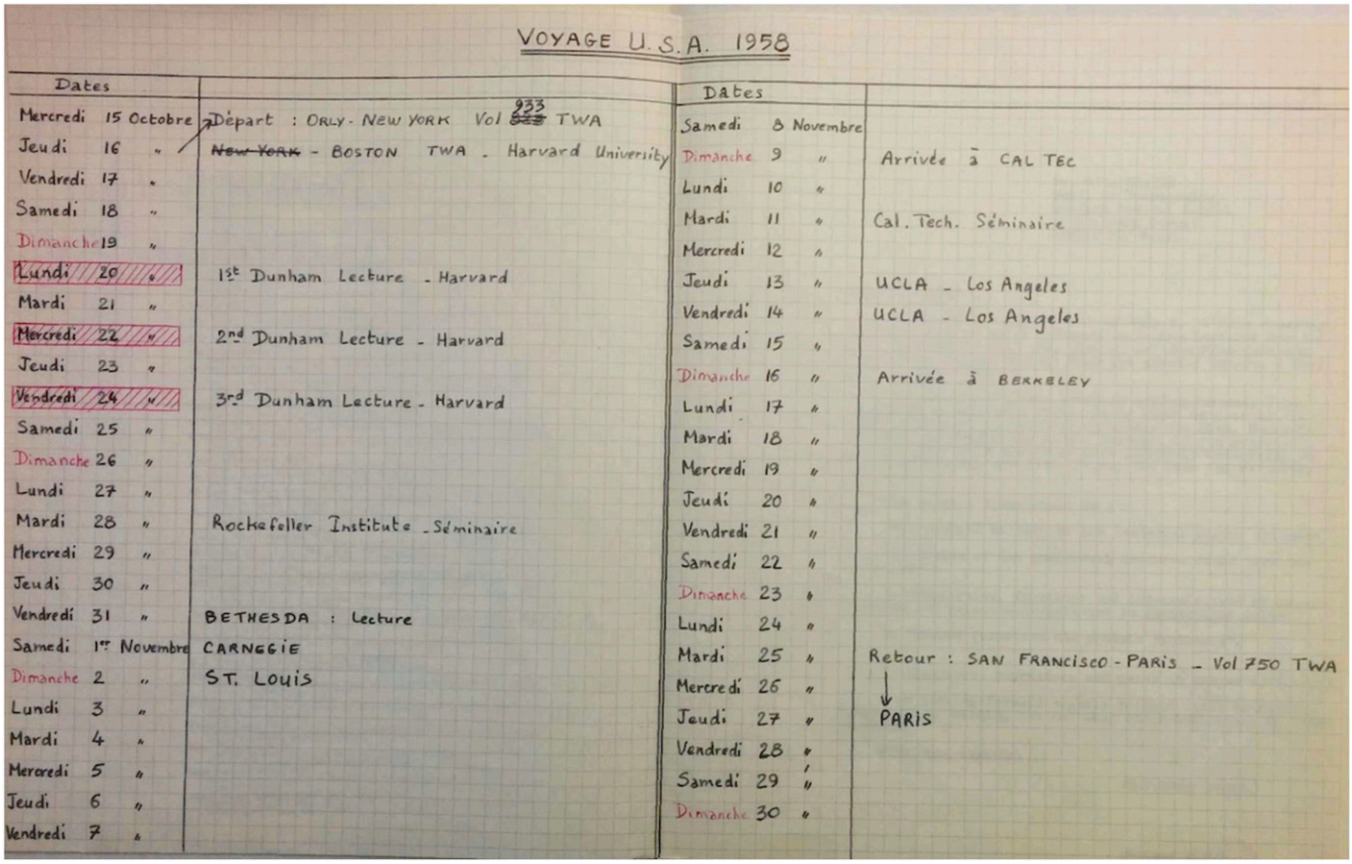
> The structure of the enzyme must therefore be entirely defined by the genome and inducer action might be described as release of activation of latent genetic potentialities [Monod 1958c, p. 1].

If Mayr had attended Monod's lecture on the genetic determinism of bacterial physiological functions using information-based explanations, he probably would have been highly interested in having a discussion with the French scientist, especially since Monod had expressed his wish to prove the purposeless behavior of living beings (Gross 1959). Directly or indirectly, it is highly probable that Mayr had the opportunity to hear about the conference and that he attended it. Moreover, Monod and Mayr shared many common friends, including Max Delbrück, James Watson, and J. B. S. Haldane.

Preparation of the Genetic Program Article

The story of Jacob and Monod's article, which introduced the genetic program metaphor and led them to receive a Nobel Prize, reveals how much Mayr and Monod had in common. It also shows the possible context from which the metaphor could have arisen. On February 9, 1960, when Monod turned 50, he was an established researcher, and his name was starting to appear every year on the list for the Nobel Prize Committee to consider (Brunerie 2009). The preceding year he had published together with Arthur Pardee and François Jacob (Pardee *et al.*1959) an article in the *Journal of Molecular Biology* outlining what is known as the "PY-JA-MA experiment" (the title being "The Genetic Control and Cytoplasmic Expression of 'Inducibility' in the Synthesis of β-Galactosidase by *E. coli*"). "PY-JA-MA" comes from the fact that the experiments were performed by Pardee-Jacob-Monod and that "PY-JA-MA" was easier to pronounce than "PA-JA-MO" (as well as being a word in English). The aim of the *Journal of Molecular Biology* was to become the leading journal in the field. John Kendrew (Kendrew 1958), its editor, wrote to Jacob to ask him to join the advisory board, and Jacob accepted. Among the other members of the board were Francis Crick, Arthur Kornberg, Salvador Luria, and Max Perutz. In May 1960, Jacob wrote to Kendrew to ask whether the journal would be interested in a review paper written by Monod and himself:

> We also feel that we should write some kind of review on the regulation mechanism operating in protein synthesis. Most of our data has [*sic*] been published in separate notes or papers. But it would probably now be useful to integrate them in a single review. This will probably be written in French and will have more than 20 pages. This will not be ready before next fall [Jacob 1960].



VOYAGE U.S.A. 1958

Dates	
Mercredi 15 Octobre	Départ : ORLY - NEW YORK Vol 933 TWA
Jeudi 16 "	~~NEW YORK~~ - BOSTON TWA . Harvard University
Vendredi 17 "	
Samedi 18 "	
Dimanche 19 "	
Lundi 20 "	1st Dunham Lecture - Harvard
Mardi 21 "	
Mercredi 22 "	2nd Dunham Lecture - Harvard
Jeudi 23 "	
Vendredi 24 "	3rd Dunham Lecture - Harvard
Samedi 25 "	
Dimanche 26 "	
Lundi 27 "	
Mardi 28 "	Rockefeller Institute - Séminaire
Mercredi 29 "	
Jeudi 30 "	
Vendredi 31 "	BETHESDA : Lecture
Samedi 1er Novembre	CARNEGIE
Dimanche 2 "	ST. LOUIS
Lundi 3 "	
Mardi 4 "	
Mercredi 5 "	
Jeudi 6 "	
Vendredi 7 "	

Dates	
Samedi 8 Novembre	
Dimanche 9 "	Arrivée à CAL TEC
Lundi 10 "	
Mardi 11 "	Cal. Tech. Séminaire
Mercredi 12 "	
Jeudi 13 "	UCLA - Los Angeles
Vendredi 14 "	UCLA - Los Angeles
Samedi 15 "	
Dimanche 16 "	Arrivée à BERKELEY
Lundi 17 "	
Mardi 18 "	
Mercredi 19 "	
Jeudi 20 "	
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Mercredi 26 "	↓
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Vendredi 28 "	
Samedi 29 "	
Dimanche 30 "	

Figure 1 Monod's planning for his travel to United States in 1958, which he sent to Otto Krayer, his host (Monod 1958c).

Kendrew accepted immediately, although stipulating that the article would have to be translated. Five months later, Jacob would send another letter: the manuscript would most likely be written in English and reach 70 pages. During the summer, Jacob was in California at Cal Tech with Sydney Brenner to perform the final experiments proving the existence of messenger RNA (Jacob 1987; Carroll 2013). Jacob had been invited to Pasadena by Max Delbrück, whom Mayr would cite extensively in his *Science* article and one of the most influential physicists in postwar biology (Morange 1994). In November 1960, Monod and Jacob started writing the article that would introduce the terms "messenger RNA" and "genetic program" to the world, and the article was finished by December. Jacob (1987, p. 428) acknowledged that Monod wrote the entire last version of the manuscript by himself because he was much more comfortable with English—his mother was American—than Jacob. Jacob also gave an account of the overall preparation of the article:

> This review painted like a fresco the history of protein synthesis and its regulation. . . . Showed for the first time how a gene worked; how it produces the continuous flow of information towards the cytoplasm. . . . Proposed a model to explain one of the oldest problems of biology: for organisms made of millions, even billions of cells, all of them own a complete set of genes; how is it then that all genes do not function in the same way in all tissues? That nervous cells do not use the same genes as muscle cells or liver cells? In short, this article presented a new perspective of the genetic landscape. . . . In the end, for Jacques [Monod] natural selection had carved each organism, each cell, each molecule in its smallest detail. ... [T]o nature, Jacques attributed Cartesianism and elegance. Which explains his taste for unique solutions. On my side, I wasn't finding the world as strict and rational [Jacob 1987, pp. 428–430].

Jacob's account reveals many things about the preparation of the paper and highlights once again the similarities with Mayr's article. The model he mentioned was the solution to the problem of differentiation that he called the "genetic program" and others would later call the "developmental program." Jacob (1987) seemed to suggest that the logic, the rationality, came from Monod, who believed that natural selection had "carved" organisms. Had the metaphor come from Jacob or from Monod? The facts that Monod had written the last version of the paper and that he seemed to have a much more Cartesian vision of the world suggest that he may have come up with it.

Once written, the manuscript was put into the hands of Madeleine Brunerie, who had to type it (Brunerie 2009). By mid-December, the two molecular biologists were getting ready for travel. Monod had been invited to India by a former student (G. P. Talwar) to give a course on the biosynthesis of macromolecules and attend a conference during

the annual meeting of the Society of Biological Chemists of India (Talwar 1960). Beyond visiting his former student, Monod was happy to travel to India for two reasons: his wife, Odette, was an archeologist and specialist of India and Pakistan, and he was happy to offer her the opportunity to go there (Brunerie 2009). Monod was also hoping to meet with J. B. S. Haldane, someone for whom he had "an unlimited respect and admiration" (Monod 1960b). Monod spent the Christmas holidays in India and came back to France in January 1961 (Brunerie 2009). While Monod was meeting Haldane, Jacob was in Cambridge, England. The article for the *Journal of Molecular Biology* was deposited directly on John Kendrew's desk on December 28, 1960, in Cambridge by Jacob (Jacob 1961). After Monod's return, they continued to work on the article, probably making corrections suggested by the reviewers (neither the Institut Pasteur nor the *Journal of Molecular Biology* have kept archives regarding this article). The paper was published in June; as Carroll (2013) writes, "[I]t would be a watershed in modern biology." In fact, while the paper was being printed, Jacob and Monod were in Cold Spring Harbor for a symposium entitled, "Quantitative Biology and Cellular Regulatory Mechanisms," where they made two presentations: "On the Regulation of Gene Activity" and "Teleonomic Mechanisms in Cellular Metabolism, Growth and Differentiation: General conclusions" (Brunerie 2009). As mentioned earlier and in sharp contrast to Mayr (1961), the concept of teleonomy is absent from Jacob and Monod (1961) probably because they wanted to separate the established experimental facts from the speculative and philosophical conclusions. But their presentation made in the summer 1961 (published later) shows that they had thought about the link between the genetic program and teleonomy. Curiously, Mayr had stated that he was the one who introduced Jacob and Monod to teleonomy (Kay 2000, pp. 221 and 369); either this is not true and is a mistaken memory, or they had indeed met before the summer 1961. On June 29, 1961, shortly after publication of the genetic program article, Monod wrote a letter to Jacob, who was on vacation in the Alps. After telling him about the progress on a new manuscript (regarding teleonomy) they were preparing, he wrote

> I have become convinced that genetic repression is probably the second big secret of life, the first one being, of course, the code and its transcription. … On the messenger itself, its isolation, its structure and its association with ribosomes, there is right now a thousand Americans and four thousands Japanese which are taking care of it. I doubt we could do better than them. Enjoy your vacation. Warmly yours. Jacques Monod [Monod 1961].

This transcribed code was probably what he and Jacob had called the "genetic program" a few months earlier. Although the genetic program metaphor was published, Monod continued to use both terms, "code" and "program," interchangeably. Had he (and Mayr) originally thought about the metaphor as a code rather than a program?

An Older Origin?

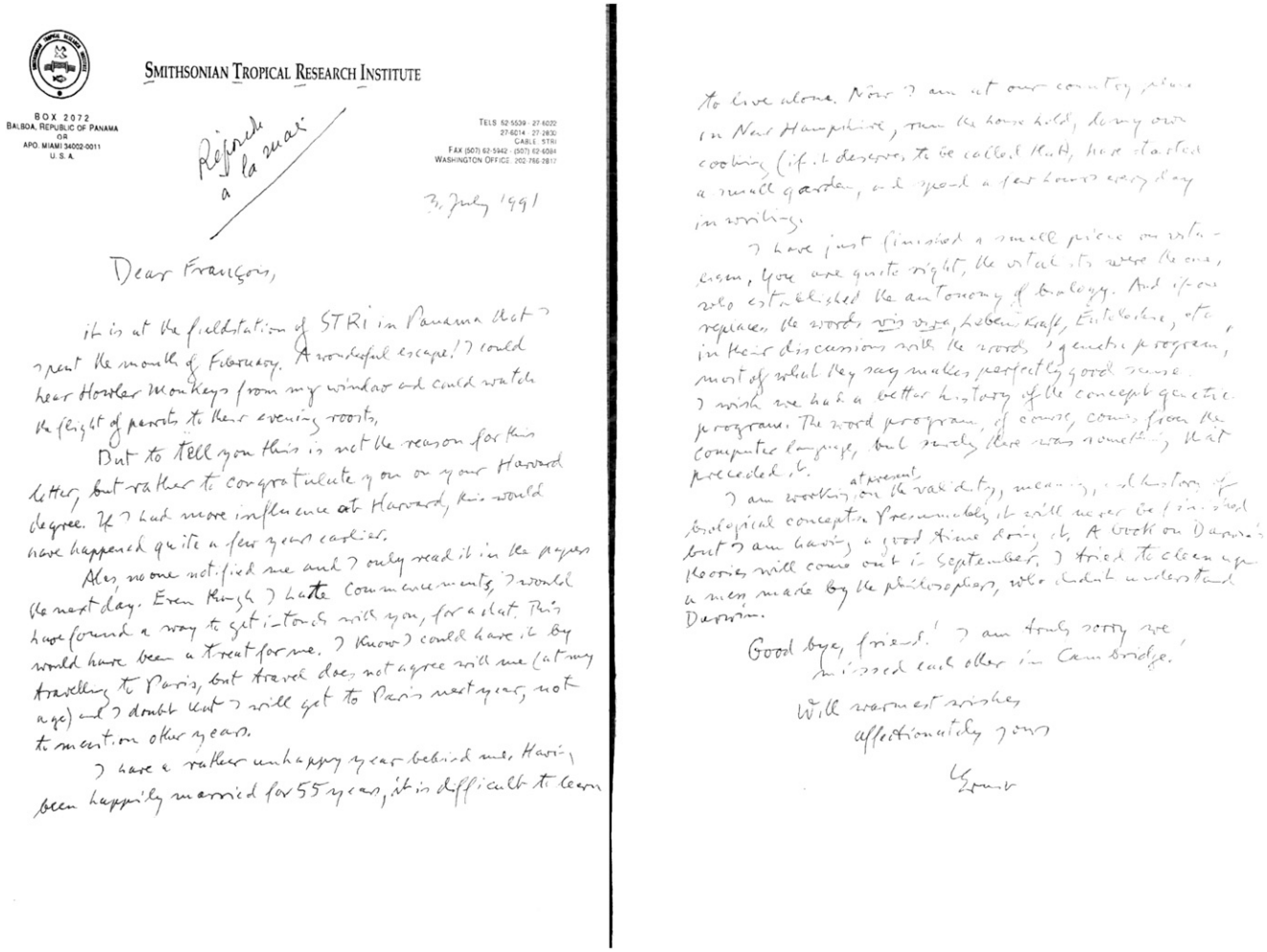
"Program" had never been used previously in the sense of "genetic program," but "code" had been used in that sense before. Among the abundance of informational metaphors that flowed from physics and computer science to biology after the war, Erwin Schrödinger's "hereditary code script" sounds close to "genetic program." This metaphor comes from Schrödinger's influential book, *What Is Life?* which has often been cited as a starting point for molecular biology. One section is entitled, "The Hereditary Code-Script (Chromosomes)," and shares a striking similarity to both Mayr's and Jacob and Monod's writings:

> Let me use the word "pattern" of an organism in the sense in which the biologist calls it "the four-dimensional pattern," meaning not only the structure and functioning of that organism in the adult, or in any other particular stage, but the whole of its ontogenetic development from the fertilized egg to cell to the stage of maturity, when the organism begins to reproduce itself. Now, this whole four-dimensional pattern is known to be determined by the structure of that one cell, the fertilized egg. … It is these chromosomes, or probably only an axial skeleton fibre of what we actually see under the microscope as the chromosome, that contain in some kind of code-script the entire pattern of the individual's future development and of its functioning in the mature state. Every complete set of chromosomes contains the full code. … But the term code-script is, of course, too narrow. The chromosome structures are at the same time instrumental in bringing about the development they foreshadow. They are law-code and executive power—or, to use another simile, they are architect's plan and builder's craft—in one [Schrödinger 1944].

In 1944, Schrödinger had already envisioned a kind of developmental program, except that he called it "code." The close similarity between the two words in common English and knowing that "code" and "program" were used interchangeably by biologists at the time could be enough to link "genetic program" to Schrödinger's "code-script." However, it is of importance that Schrödinger never linked this program to evolution, something essential for Mayr and later for Monod and Jacob. Nevertheless, it is legitimate to wonder why he is not cited in Mayr's and Jacob and Monod's articles? Jacob acknowledged that he encountered that book only late in his life and that he does not recall being particularly influenced by it (Morange 2002, pp. 59–60). The word "program" is absent from Schrödinger's essay. It is even possible to suggest an older influence from Descartes, who wrote

> If we knew well which are the part of the seed of any species of animal, men for example, we could deduce, from entirely mathematical reasons and certain, all the figure and conformation of each of its parts and conversely, by knowing many particularities of this conformation, we could deduce which is the seed [Descartes 1984, p. 277].

Hence, more than 300 years earlier, Descartes had already come close to the genetic program metaphor, although he lacked the essential concept of information. This statement is close to Schrödinger's and may have influenced the latter



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Répondre à la main
à

31 July 1991

Dear François,

it is at the fieldstation of STRI in Panama that I spent the month of February. A wonderful escape! I could hear Howler Monkeys from my window and could watch the flight of parrots to their evening roosts.

But to tell you this is not the reason for this letter, but rather to congratulate you on your Harvard degree. If I had more influence at Harvard, this would have happened quite a few years earlier.

Alas, no one notified me and I only read it in the papers the next day. Even though I hate commencements, I would have found a way to get in touch with you, for a chat. This would have been a treat for me. I know I could have it by travelling to Paris, but travel does not agree with me (at my age) and I doubt that I will get to Paris next year, not to mention other years.

I have a rather unhappy year behind me. Having been happily married for 55 years, it is difficult to learn to live alone. Now I am at our country place in New Hampshire, run the household, do my own cooking (if it deserves to be called that), have started a small garden, and spend a few hours every day in writing.

I have just finished a small piece on vitalism, you are quite right, the vitalists were the ones who established the autonomy of biology. And if one replaces the words *vis vitae*, Lebenskraft, Entelechie, etc in their discussions with the words "genetic program", most of what they say makes perfectly good sense.

I wish we had a better history of the concept genetic program. The word program, of course, comes from the computer language, but surely there was something that preceded it.

I am working on the validity, meaning, and history of biological concepts. Presumably it will never be finished but I am having a good time doing it. A book on Darwin's theories will come out in September. I tried to clean up a mess made by the philosophers, who didn't understand Darwin.

Good bye, friend! I am truly sorry we missed each other in Cambridge.

With warmest wishes
affectionately yours

E Mayr

Figure 2 Ernst Mayr's letter to François Jacob in 1991 from Panama. Jacob wrote on the letter "Repondre à la main" (Answer with a hand-written letter). The answer is neither in Jacob's nor Mayr's archives. Mayr was not at Harvard at this time, and Jacob rarely kept a single copy of the letter he sent (personal communication) (Mayr 1991).

(Morange 1994). Five years after Schrödinger, Henry Quastler wrote with Sidney Dancoff a paper entitled, "The Information Content and Error Rate of Living Systems." The authors had benefited from comments on the manuscript from Salvador Luria and Aaron Novick (Kay 2000), researchers who were friends of both Monod and Mayr. The article mentions "a linear coded tape of instructions" and draws an analogy between a written message and the chromosome. From that the authors derived a calculation of the information content of living beings. As reported by Kay (2000), Quastler organized a symposium entitled, "Information Theory in Biology," in 1952:

> Another participant, Kenyon Tweedell, analyzing the development of zygotes and identical twinning, praised information versus epigenesis: specificity corresponded to preformation, epigenesis to nonspecificity. He wrote "The information content is a set of instructions coded in the fertilized egg as dictated by genetic constitution; if a section of the instruction happens to lie in the zone which will give rise to the part to which this section refers, the part will behave as if preformed. This argument preceded François Jacob's analysis of the "genetic program" and Delbruck's information reinterpretation of Aristotle's theory of generation by more than a decade [Kay 2000, p. 122].

These writings suggest the possibility that the metaphor was already in use before 1961 and that interacting with the same groups of biologists, Mayr and Jacob and Monod would have heard it somewhere. The fact that they never mentioned that they were the initiators of the metaphor is in agreement with this later possibility. After Mayr's visit to the Collège de France, where Jacob had become a professor, the two scientists continued to interact, especially on their idea about the genetic program. Mayr had come to consider that Jacob was the greatest biologist of the twentieth century (Gayon 2012, p. 13). In 1991, Mayr spent a year at the Smithsonian Tropical Research Institute in Panama, which he called "a wonderful escape." From there he sent a letter to Jacob (Figure 2), the ending of which is very surprising:

> I have just finished a small piece on vitalism; you are quite right, the vitalists were the ones who established the autonomy of teleology. And if one replaces the words *vis*,

> *vita*, . . . *entelechie*, etc. ... in their discussion with the words "genetic program," most of what they say makes perfectly good sense. I wish we had a better history of the concept of the genetic program. The word program, of course, comes from the computer language, but surely there was something that preceded it (Mayr 1991).

The letter ends with a warm "Good bye friend!" Had Mayr forgotten that he was part of the story of the genetic program? Or did he realize that when he used that metaphor in 1961 he had gotten it from somebody else? Unfortunately, Jacob's answer cannot be found in either of the two scientists' archives.

It seems very likely that before 1961, the metaphor was already "in the air." Mayr and Monod and Jacob were simply the first to mention the genetic program explicitly. This does not imply that we should relentlessly look for the precursor who really introduced the metaphor. French philosopher G. Canguilhem has warned us against such approach in the history of science (Canguilhem 1983), which confuses the object of the history of science with the object of science itself (Rheinberger 2005). Rather, we should try to understand the metaphor of the genetic program as an object of the history of science and not exclusively as the precursor of what we call today the "genetic program." In the 1960s, the genetic program metaphor played a crucial role in biology and helped to clarify many issues in the field. However, metaphors that "illuminate matters quickly and efficiently" may dim "with time and frequent usage" (Wilkins 2013) until they no longer capture the complexity of the field to which they belong. Whether this is the case regarding the genetic program metaphor is still an ongoing debate.

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