REMARKS ON FRANÇOIS JACOB'S CONCEPT OF INTEGRON

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In this article, the concept of integron as it appears in François Jacob's book *The Logic of Life* is discussed. It begins by locating the concept within the overall structure of Jacob's book. The book is conceived as a history of heredity, with the central historical chapters framed by an epistemological discussion of the notions of program in the introductory chapter and of integron in the concluding chapter. A detailed analysis of the concept of integron follows, including that of reproduction on which it relies. It is then compared with the concept of hypercycle as developed around the same time by Manfred Eigen and Peter Schuster. The article concludes on a note on name-coining in the sciences with a focus on Jacob's own practice.

1. Introduction

In 2020, François Jacob's *La Logique du vivant* turned 50 years old. The following remarks can be read as an addendum to the historical and conceptual analysis of Jacob's book that Pierre-Olivier Méthot (2020, 2023) presented on that occasion and in his paper in this special issue. In contrast to Méthot's encompassing analysis, this short contribution concentrates on a single concept that Jacob introduced as a neologism in his book: the integron.[1]

To understand its strategic position in the book, I briefly outline the overall structure of *The Logic of Life*. Its character is unique: The central chapters of the

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1. It should be pointed out that today in molecular biology, the term "integron" has acquired a specific meaning that is distinctly different from Jacob's use of the term. It designates versatile gene acquisition systems found in bacterial genomes (Mazel 2006).

Electronically published September 21, 2023.

HOPOS: The Journal of the International Society for the History of Philosophy of Science, volume 13, number 2, Fall 2023. https://doi.org/10.1086/726253

book are historical in nature and roughly follow a chronological trajectory through the history of the life sciences from the early modern period to the heydays of molecular biology. Each chapter stands under the generalized notion of an object that can be addressed as embodying an organizing concept in the respective time period under consideration: The succession reaches from the visible structure to the invisible organization, to the gene, and finally to the molecule. Each of these objects, or levels of analysis, is seen to have become accessible through a specific constellation of approaches that became possible by the introduction of methods characteristic for the period under consideration. Together, these chapters are framed by an introduction captioned "The Program" and an epilogue carrying the title of "The Integron." These introductory and concluding chapters are programmatic rather than historical in character. They try to convey what Jacob then perceived as the essential categories that molecular biology was about to establish for an understanding of the world of the living. Although a certain image of the process of biological evolution clearly informs Jacob's assessment of the historical path of the life sciences, he carefully tries to avoid the then fashionable reductionist model of "mutation and selection" (Monod 1975; Popper 1975, 1979). He favors foregrounding not a particular mechanism but the open, ateleological character of scientific development, as succinctly expressed by Thomas Kuhn (1970, 170) in his book *The Structure of Scientific Revolutions*, when claiming to have written about a process of evolution *from* but by no means *toward*.

Many discussions have taken place around the concept of program. There was a time when it was criticized as the paragon of molecular biology's new reductionism (Sarkar 1996; Fox Keller 2000; Kay 2000). It became a bête noire for a generation of philosophers of biology who saw molecular biology's conceptualizations as the culmination of a long period of writing the organism out of the history of biology. A more recent essay usefully traces the historical origin of the concept (Peluffo 2015). Jacob (1970) thought of it as rescuing the life sciences from their reduction to physics and chemistry: "One can do no biology anymore without constantly referring to the 'project' of the organisms, to the 'meaning' that their mere existence conveys to their structures and functions. One sees how much this attitude differs from the reductionism that has for a long time prevailed" (321). And he summarized the basic idea behind this statement with the following words: "There is only the incessant execution of a program inseparable from its realization. For the only elements that are able to interpret the genetic message are the products of that message. The genetic text has a meaning only for the structures whose nature it has determined. With that, there is no longer an origin to reproduction; there is only a cycle of events in which each of its constituents can fulfill its task only in relation to the others"

(318). Jacob thus interprets the findings of molecular biology as a means of overcoming a view of the organism that is reductionist in the sense that it reduces it to the image of mere interplay between mechanical forces, all while firmly abstaining from anything like vital principles. For him, the language of molecular biology allows for looking at organisms as meaningful entities in themselves.

2. The Concept of Integron

Taking the above quotes as a starting point, we are ready to enter into a discussion of the concept of integron that organizes and dominates the book's concluding remarks. The discussion will then be followed by a glance at the hypercycle, a concept developed by Peter Schuster and Manfred Eigen in Göttingen at roughly the same time and in parallel in the course of the 1970s. I conclude this brief essay with a short note on coining terms in the sciences—an art cultivated and held in high esteem by Jacob and the Lwoff laboratory to which he belonged—its possible crystallizing function, and the fate of the concept of integron.

Let us begin with Jacob's (1970) definition: The "general term of integron" designates a "cycle of events in which each of its constituents can fulfill its task only in relation to the others" (323). What remains difficult to understand, Jacob confesses in the longer passage where he introduces the concept, is "the appearance of an integrated system of a most primitive kind, that is, the origin of an organization capable of reproduction, as bad and sluggish as it may be" (326). Once the system works, so it appears, it leaves no trace of its origin. I come back to this point on the occasion of the discussion of Eigen and Schuster's (1979) hypercycle later. We see that this "originary" integration, as we may call it, is intimately connected to the concept of reproduction as the basic characteristic of the living: "To reproduce is not in the ability of any molecule alone. This faculty only appears with the simplest of integrons deserving the qualification of being alive" (Jacob 1970, 328). From this short description, it becomes clear that the concepts of integron, program, and reproduction are intimately linked. If reproduction is to be taken as the basic feature of organic life, its self-procreation, then the notion of program aims at conceptualizing the process at the molecular level; with the notion of integron, Jacob tries to capture its phenomenology.

Jacques Derrida undertook a lengthy, critical conceptual analysis of Jacob's (1970) *The Logic of Life* in his seminar on *La Vie la mort*, held in the winter of 1975–76 and largely unpublished until 2019. In particular, Derrida (2019) complained that Jacob failed to subject what he saw as the "major operational, ultimate concept of his discourse" (135; see Vitale 2018)—that is, reproduction—to a

thorough critique. Curiously enough, Jacob used this term, which was so central for the theoretical message of his book, with the rather colloquial meaning that we attribute to the term when we talk generally about the propagation of living beings, their capacity for re-creating themselves, more or less synonymously for a number of different processes: the molecular replication of DNA, the coded molecular assembly of proteins, the division of bacterial cells, and the sexual propagation of higher organisms. Because the capacity to reproduce is, according to Jacob, the grounding feature of the basic integron, the intuitive and qualitative use of the term "reproduction" bemoaned by Derrida also affects the usage of the concept of integron itself.

From this starting point—"the simplest of integrons"—onward, Jacob (1970) sees biological evolution proceeding through what he calls a "series of integrations" (327). We realize that here again, we have to do with a conceptual slippage. Jacob himself is aware of this fact: "From now on," he contends, "the rule of the game is modified" (328). From now on, so it appears, integrons no longer simply designate a reproductive cycle but rather indicate what is usually called, and what Jacob himself calls, "levels of organization" (328), as ever more composite, integrated units of structure and function: cells, multicellular organisms, populations, ecosystems, even up to "cultural and social integrons" (341)—you name them. What is most important in this context is that each of these levels exhibits new, previously nonexistent qualities; and yet, the overall necessity to sustain and favor reproduction in one way or the other underlies them all. "What unites the different levels of biological organization is the logic proper to reproduction. What distinguishes them are the means of communication, the circuits of regulation, the internal logic proper to each of the systems" (Jacob 1970, 328). And Jacob does not forget—and is careful enough to add—that the cultural and social integrons are "beyond the explanatory schemes of biology" (342).

The conundrum of the construction of such a succession is, how do we get from one level to the next? It appears as if the unanswerable question of the origin would become repetitive. Interestingly enough, Jacob never uses the notion of emergence in the context of his description, and in his later work, he uses it extremely sparingly. In his essay on *The Possible and the Actual*, for instance, the term appears only once in the context of a discussion on the origin of life and the origin of what "we call mind" (Jacob 1982, 59). Instead, he insists on the material continuity of the evolutionary process. The keyword remains "integration," a term reciprocally related to those of "organization" and "emergence," as Georges Canguilhem (1971, 25) stressed in his thoughtful review of Jacob's book, summarizing with this conceptual triple the content that Jacob (1970) himself expressed in the last pages of his work: "It is through integration that the quality of things changes. An organization often exhibits properties that do not exist

at a lower level. These properties can be explained by those of its constituents, but not deduced from them. A particular integron has thus only a certain probability to appear" (344). Thus, there remains an irreducible moment of contingency. Evolution is punctuated by contingent events that not only lead to material integratory reorganizations but also—and necessarily so—need to be integrated into the explicatory schemas that aim at making sense of them: "Today, it is thus on contingency that the unit of explication rests" (Jacob 1970, 345).

We have to be attentive to the wording here. The qualifier "today" is consciously chosen in this sentence. Throughout the book, Jacob tells a *history* of conceptualizing the living, and he tells it as a succession of *conceptual integrations*, as we might call them. Neither of them could be deduced from the foregoing one, although each could be explained by the elements—technical and epistemic, instrumental and conceptual—that went into them. Thus, although Jacob does not explicitly verbalize it in *The Logic of Life*, as he does later in his slim volume on *The Possible and the Actual* (Jacob 1982), we see that he conceptualizes the history of knowledge as a punctuated process of evolution. Nevertheless, he carefully avoids any direct comparison with biological evolutionary mechanisms (Méthot 2023, in this issue), a trap into which his colleague Jacques Monod walked in the footsteps of Karl Popper. In the conclusion of *The Logic of Life*, Jacob (1970) consequently subjects his own vision as of "today" to a historical caveat: "Today the world is message, codes, information." And he goes on, asking, "What kind of dissection will displace our objects and recompose them in a new space tomorrow?" (345).

Around the time Jacob struggled with his concept of integron, Manfred Eigen and his associate Peter Schuster in Göttingen were working out their concept of the hypercycle (Eigen 1971; Eigen and Schuster 1979; cf. Maynard Smith 1979). It can be regarded as a mathematically formalized version of Jacob's qualitative notion of integron. As the hypercycle concept describes a basic molecular mechanism by which two synthetic processes are integrated into a mutually enhancing superstructure, presenting it briefly will contribute to a better understanding of a fundamental mechanism of attaining qualitatively different levels of organization in the process of organic evolution. And it shows that this question was experienced as being of a particular urgency at the time and that Jacob, among others, felt himself pressed to answer it.[2]

Eigen (1987) speaks of an "integration of replicators" (229). His paradigmatic example is the integration of nucleic acids and proteins: nucleic acid catalyzes

2. I could also have added here, by switching to a more complex level of organization, the contemporary efforts of Lynn Margulis (1970) to explain the symbiotic emergence of eukaryotic cells.

the production of a replication enzyme, which in turn catalyzes the production of more nucleic acid of the same type. The point is that if contained in a compartment, a hypercycle—in contrast to an autocatalytic cycle that grows exponentially—tends to reproduce hyperbolically and thus outgrow its separated predecessors.

This short exposition shows clearly that "the molecular vision of life" in general, as Lily Kay (1993) once aptly called it, and the vision of molecular genetics in particular, held by proponents such as Jacob or Eigen, by no means displays that ultra-reductionistic attitude of which organismically and holistically inclined critics have tended to accuse it. In contrast, they spent much effort to come to terms with the double challenge to, on the one hand, exclude any hidden vital forces from their discourse and, on the other hand, to maintain "life's irreducible structure," as Michael Polanyi (1968) then put it. I will not expand on the reductionism debate further in this article. Meanwhile, the debate has lost much of its earlier drive and impact. The reason appears not least to lie in the development, over the past decades, of the life sciences themselves (see, e.g., Rheinberger and Müller-Wille 2017).

3. Conclusion

Instead, I would like to close with a note on coining names. Jacob was well aware—and in this he was in good company with many of his colleagues, in particular the cohort of first-generation molecular biologists to which he belonged—that finding a fitting expression for an intriguing phenomenon is not of minor importance for a scientist seeking recognition among their peers. In his autobiography, Jacob (1988, 283) reports that his teacher André Lwoff had installed a "terminology committee" in his unit at the Pasteur Institute in Paris that was called into action whenever a new entity or a new phenomenon appeared in the course of their experiments (see Morange 2005). Then he vividly describes how the protein coat of a virus was termed "capsid" and its units "capsomeres" (Lwoff, Anderson, and Jacob 1959), two notions that stuck and that are still in use today (Cann 2015). A similar story could be told about the notion of "operon" that Jacob and Monod introduced in 1960 to designate a chromosomal genetic regulatory unit in bacteria (Jacob et al. 1960). Another example is the sexual factor that determines whether a bacterium acts as a receptor or as a donor in the process of bacterial genetic transformation. The mechanism would form the basis of the later experiments that led to the identification of messenger RNA shortly thereafter. The group baptized it "episome" (Jacob and Wollman 1958), an expression that was used for quite a while in the literature and eventually was given up in favor of the term "plasmid," which is still current today. Mathias Grote

(2008) has devoted an illuminating paper to this terminological transition. Jacob (1988) aptly pointed to the assuring function of naming in the experimental process—and its danger at the same time—when stating that "thus named, things immediately took on a new reality. They existed!" (284).

Examples abound. To stay with only Jacob, more could be adduced, such as the notorious "messenger RNA" (Pardee, Jacob, and Monod 1959). He as well as Monod and Lwoff were masters in that game. But we have to differentiate. Generic terms can differ in their function, and they can come with different conceptual loads. We can distinguish terms that predominantly serve the function of name-giving and, as such, can easily be replaced. The episome would be a case in point. We can further distinguish terms that have a more or less organizing and operational function in the research process. The concept of operon would clearly fall in this category: It can be used as a guiding principle in experimentation and, as such, can fail or stand the test. Initially, it was a concept that applied to bacterial genomes, and it remained so. As it turned out, the genome of higher organisms did not exhibit comparable features.

Still another category may be designated as "generalizing terms." They bring different phenomena that share a particular feature under an overarching heading. If overgeneralized, they may lose their function in scientific research, be it that of reality stipulation (e.g., the episome) or that of conceptual guidance for experimental exploration (e.g., the operon). They become subsumptive in the merely classificatory sense of the word, and thus their operational power is lost. This seems to have been the case with the notion of integron. We can assume that it was for this reason that the term never entered the collective discourse of molecular biology in either of these functions—neither terminological nor operational—and on either of the levels at which they are located. And it appears that Jacob himself was plainly aware of this shortcoming, as he never took the notion up again in his later writings, in either *The Possible and the Actual* (Jacob 1982) or *Of Flies, Mice, and Men* (Jacob 1998). However, he never dropped it explicitly either. For once it seems, Jacob did not succeed in condensing a problem into a new category that was to stay. The phenomenon, however, that had motivated his effort continued to occupy a central and increasingly prominent place in the life sciences, as molecular genetics became gradually embedded in a molecular biology of the cell.[3]

3. At the time, that transition was epitomized by the morphing of James Watson's (1965) textbook on *Molecular Biology of the Gene* into *Molecular Biology of the Cell* (Alberts et al. 1983).

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