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The mechanistic-holistic divide revisited: The case of the *lac* operon

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ABSTRACT

In this paper, I revisit the development of the repression model of genetic regulation in the *lac* operon to challenge a common application of a conceptual framework in the history of biology. I take Allen's (1978) account of the changes in the life sciences during the early and mid-twentieth century as an example of a common application of a framework based on the dichotomy between a mechanistic, or reductionist, approach to science and a holistic one. From this conceptual framework, Allen infers two general claims about the process of science and its goals: (1) that "mechanistic materialism" has often presented a more practical way to begin the study of complex phenomena in the life sciences, and (2) that the approach described as "holistic materialism" provides a more complete or accurate description of the natural world. The development of the *lac* operon model does not fit Allen's generalizations about scientific developments, and it can be used to cast some doubt on the scope of application of that conceptual framework. I argue that a better framework to interpret particular episodes in the history of molecular biology is to consider the ways in which biologists prioritize and track different aspects of the phenomena under study, rather than to focus on whether certain scientific practices are best described as developing from mechanistic to more holistic approaches. I end with some implications for the historiography of science by considering the appropriateness of different conceptual frameworks for different grains of resolution in the history of biology.

1. Introduction

The history and philosophy of science requires a conceptual framework with which to interpret the significance of scientific events or periods, the emergence and acceptance of scientific theories, concepts, models, and metaphors, and the multiple lines of influence between scientists, institutions, and ideas. Most philosophers and historians adopt or develop conceptual frameworks and defend these frameworks as useful for understanding the nature of scientific change or for illuminating some aspect of scientific practice. That has been the case for many scholars addressing episodes in the history of molecular biology, especially the significance of the molecular turn in mid-20th century biology and the entrenchment of certain concepts, such as the genetic code and the genetic program. Some major works that have illuminated these aspects of molecular biology include Allen (1978), Jacob (1970), Judson (1979), Kay (2000), Morange (1998), and Olby (1974).

Often, in these works and elsewhere, episodes in the history of molecular biology are interpreted in terms of shifts from a reductionist or mechanistic approach to studying phenomena to a non-reductionist or holistic one. This framework has been used to explain transformative periods in the history of modern biology, such as the early contributions of biochemistry, physiology, and genetics to molecular biology (Allen, 1978), and shifts to new problems in molecular biology, such as the role of genetic regulation in cellular differentiation and the developmental programs of multi-cellular eukaryotes (Morange, 1997). The framework appears again after the completion of the Human Genome Project to address emerging questions about how to study the functions of non-coding DNA in the post-genomic era (Keller, 2005; Woese, 2004).

In this paper, I focus on Garland Allen's influential account of the key shifts in particular research traditions within twentieth century biology to illustrate the conceptual framework at work. Influenced by a dialectical materialist view of historical progression, Allen represents episodes in the history of science through dichotomies and views scientific change as a series of discontinuities and revolts. Allen uses a dichotomy between "mechanistic materialism" and "holistic materialism" to interpret the developments in the fields of physiology, biochemistry, and genetics, all of which converged to form the field of molecular biology in the mid-twentieth century. Imposing this lens on the developments in twentieth century biology leads Allen to make two general

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inferences about the nature of scientific practice; (1) that "the mechanistic approach has often been the only practical way to begin the study of a complex process," and (2) that the approach described as "holistic materialism" aims to provide a more complete and accurate description of the natural world (Allen, 1978, 105–016). Because Allen's view has been influential and continues to receive attention, it is worth looking more closely at his framework in order to get at the implications of thinking about the history of the life sciences in the ways he suggests.

I argue that his generalized claims about scientific practice are doubtful when looking closely at the practices within a particular research program, such as those used by scientists working on the problem of enzyme induction in the labs of the Pasteur Institute during the mid-twentieth century. To defend this claim, I first present a historical analysis of the development of the *lac* operon model in molecular biology. I then present a critical review of Allen's conceptual framework and his generalizations about scientific developments. I argue that a close look at the scientific practices in early gene expression research depicts an iterative and integrative process that does not progress from a mechanistic or reductionist approach towards a more holistic approach. And, it also presents a challenge to the assumption that the holistic or anti-reductionist approach to representing phenomena is inherently more complete or complex. I offer an alternative framework based on the notion of tracking processes to interpret and analyze episodes in the history of molecular biology in the following section. This alternative considers the ways in which biologists track and prioritize different aspects of biological phenomena over time. I argue that this framework is more useful for the purpose of shedding light on the nature of the conceptual and experimental practices in particular episodes within the history of biology. Finally, I consider some implications for the historiography of science by reflecting on the appropriateness of different conceptual frameworks for different grains of resolution in the history of biology.

2. The development of the *lac* operon model

In this section, I present a study of the concepts and methods used by François Jacob and Jacques Monod (and their colleagues) to construct and justify their model of genetic regulation in bacteria. As is well documented, the Pasteurian scientists made use of many different experimental methods and techniques throughout their collaboration, including crossbreeding methods from classical genetics and induction techniques from biochemistry, as well as conceptual tools and metaphors from cybernetics. I first briefly outline the research projects on which Jacob and Monod were working to explain how the problem of bacterial gene expression arose. I then show how their experimental designs resulted from a convergence of their previous research projects. Finally, I outline how they developed and justified their model to represent the regulation of the *lac* operon system in *E. coli*. The case will be used to emphasize the integrative and iterative nature of the scientific practices involved, and to challenge Allen's general claims about the process of science and its goals.[1]

2.1. Jacob and Monod's path to the problem of bacterial enzyme induction

During the 1950s, many researchers at the Pasteur Institute focused their research on lysogenic bacteria (or lysogeny). A lysogenic bacterium is a bacterium infected by a phage, or virus, referred to as a bacteriophage. A phage infects a bacterium and inserts its genetic material, which is composed of either RNA or DNA, into the bacterial host cell's DNA. Within the host cell, the bacteriophage can have two different life cycles. During the lysogenic cycle, the bacteriophage that infects the bacterium is referred to as temperate, or non-virulent, because it does not immediately result in the lysing (destruction) of the bacterial cell. When the bacteriophage inserts its genetic material into the host cell's DNA, it is referred to as a prophage. The prophage's genetic material is then replicated with the rest of the genetic material of the host cell as the bacterium reproduces itself. However, the temperate bacteriophage has the ability to switch to the lytic, or virulent, state under certain conditions. The lytic cycle occurs when the bacteriophage's genome directs the synthesis of enzymes that lyse the bacterial cell, essentially killing the host cell, allowing its progeny phages to disperse and infect other bacterial cells in the surrounding environment (Racine, 2014).

When Jacob joined André Lwoff's laboratory at the Pasteur Institute in 1950, his main focus was the phenomenon of prophage induction, or how the phage shifts from the lysogenic to the lytic state (Jacob 1972 [1965], Kay, 2000, 208).[2] While in Lwoff's lab, Jacob worked with Élie Wollman on bacteria and bacteriophages, with a focus on the temperate lambda phage (λ-phage) in a particular strain of *E. coli*, *E. coli* K-12. They studied the cellular and genetic properties of lysogenization and virulence, and mapped the *E. coli* K-12 genome using crossbreeding techniques, which they published in 1959, in *La sexualité des bactéries* (Jacob & Wollman, 1959; Racine, 2014; Wollman & Jacob, 1956).

Within their research, Jacob and Wollman performed bacterial conjugation experiments (i.e. chromosomal transfers between bacteria), which led them to observe a phenomenon they called zygotic induction (Wollman & Jacob, 1956). In their experiments, they transferred the chromosome from a donor lysogenic bacterium, referred to as male, into a receptive non-lysogenic bacterium, referred to as female. During this process, the receptive bacterium becomes temporarily partially diploid, referred to as a merozygote, because it possesses two copies of the chromosomal segments (Grmek & Fantini, 1982; Kay, 2000; Schaffner, 1974; Wollman & Jacob, 1956). Jacob and Wollman noticed that the transfer of genetic material induced the lytic cycle in the receptive merozygotic bacterium, and so, they named the phenomenon "zygotic induction" to draw attention to the *induced* lytic state in the *merozygotic* bacterium (Grmek & Fantini, 1982, 200). From these experiments, Jacob and Wollman also established that the chromosome from the donor entered the receptive bacterium in a linear and unidirectional way, at a constant rate (Wollman & Jacob, 1956). They did this by interrupting the process of chromosome transfer between bacteria at different time intervals with the help of a Waring blender. These interventions would sever the chromosomes at different locations during the process at different time intervals, which served to create a genetic map of the bacterial chromosome. Thus, their series of experiments on lysogenic bacteria enabled the researchers to localize the phage's genetic material on a precise segment of the bacterial chromosome, and to establish that the phage's genes were immediately expressed after entering the receptive bacterial cell.

Jacob's work on lysogeny during the 1950s and his experimental knowledge of bacterial conjugation proved instrumental in his later

[1] Although Allen does not specifically address this episode in the history of molecular biology, it is an exemplar of the scientific practices adopted in molecular biology during this period and subsequent decades.

[2] Their research on lysogeny was influenced by the rich tradition in microbiological work conducted by their predecessors at the Pasteur Institute (Burian & Gayon, 1999).