Intervention as both Test and Exploration: Reexamining the PaJaMo Experiment based on Aims and Modes of Interventions

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Abstract

This paper explores multiple experimental interventions in molecular biology. By "multiple," we mean that molecular biologists often use different modes of experimental interventions in a series of experiments for one and the same subject. In performing such a series of experiment, scientists may use different modes of interventions to realize plural goals such as testing given hypotheses and exploring novel phenomena. In order to illustrate this claim, we develop a framework of multiple modes of experimental interventions to analyze a series of experiments for a single subject. Our argument begins with a brief characterization of Craver and Darden's taxonomy of experiments, because the taxonomy they have made implies various modes of interventions (Carver and Darden 2013). We propose to extract two interventional directions and two interventional effects from their taxonomy as the basis of classification. The vertical or inter-level direction means that an intervention is performed between different levels of organization and the horizontal or inter-stage direction means that an intervention is performed between different stages of a mechanism. Interventions may produce an excitatory or an inhibitory effect. As a consequence, we can classify modes of interventions according to different directions and effects. We illustrate our claims by doing a case study of the PaJaMo experiment, which is a series of experiments for a single subject. The final goal in this paper is to provide a taxonomy of characteristics of experimentation in which the PaJaMo experiment is adequately located.

Keywords: Intervention, Exploration, Experimentation, the PaJaMo experiment, Scientific Practice

1. Introduction

The molecularization of biology has raised a range of new questions and issues for the philosophy of biology, especially questions about the uses of experiments and interventions. For example, how interventional experiments contribute to discovering new phenomena and adding new knowledge in molecular biology, what experimentally causal reasoning is used in identifying mechanistic components that are responsible for some phenomenon, whether or not there are different kinds of interventions can be discerned, and how many kinds of interventions utilized by molecular biologists. These questions are important, because molecular biology is basically an experimental science and uses interventional method in almost all of experiments. More particularly, molecular biologists often use a series of organized experiments for exploring a single subject. By performing that series of organized experiments, they realize plural aims and attain plural outcomes. How do molecular biologists design and organize a series of experiments for a single subject? In order to answer these questions, the best way is to examine an actual complicated experiment in the history of molecular biology.

The PaJaMo experiment performed by Arthur Pardee, Francois Jacob, and Jacque Monod, is one of the most famous experiments in the history of biology (Craver and Darden 2013:138). Philosophers of biology such as Kenneth Schaffner (1974a, 1974b, 1993) and Marcel Weber (2005) examine it from the perspective of theory generation; and Carl Craver and Lindley Darden (2013) also analyze the experiment from the perspective of testing and discovering schemas of mechanisms.[1] Their contributions offer much help in our understanding of this famous experiment. In this paper, we would like to add a new understanding from the perspective of experimental interventions for realizing both testing and exploration aims.

Testing is a recognized aim of making experiments. In the end of the 20th century, exploratory uses of experimentation have been explored (Burian 1997; Steinle 1997). Philosophers tends to make a dichotomous distinction between testing (or theory-driven in Steinle's term) experimentation and exploratory experimentation. However, we wonder whether or not there is a kind of experiments that are both testative and exploratory. Waters (2004, 2008) provides a non-theory-centric methodology which combining explanatory reasoning and investigative strategies for classical and molecular genetics. Although Waters did not analyze experimental interventions in details, his work can serve well as an exemplar for us to develop a similar analysis on the interventions in the PajaMo experiment.

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[1] Darden and Craver have drawn attention to the discovery of a new and key component in the mechanism of protein synthesis in the PaJaMo experiment (Darden and Craver 2002). On their account, the discovery of messenger RNA (presumed to be ribosomal templates) required the integration of aspects of the mechanism by interfiled. Molecular biologists studied forward from the DNA to the next stage in protein synthesis while biochemists worked backward from peptide bonds to activated amino acids (Darden and Craver 2002:80-84). However, they don't analyze the PaJaMo experiment in details nor focus on the notion of experimental interventions.

Mechanistic philosophers such as James Woodward (2002)[2], Craver (2007), and Craver and Darden (2013) have widely analyze experimental interventions, connecting them with the analyses of mechanisms. From the view of new mechanical philosophy, knowledge of mechanisms is necessary for understanding, predicting, and controlling biological phenomenon (Machamer, Darden, and Craver 2000; Darden and Craver 2002; Glennan 2002; Bechtel and Abrahamsen 2005; Darden 2006). Experimental interventions are used by molecular biologist as powerful instruments to help produce knowledge of biological mechanisms (Machamer, Darden, and Craver 2000:17). Carver and Darden (2013) further distinguish various types of experiments in which a taxonomy of interventional modes is implied. Inspired by the pioneering philosophers' work, we intend to make the implicit taxonomy of interventional modes explicit and to inquire whether or not different modes might be used together in a series of organized experiments for both test and exploration.

A taxonomic framework of modes of experimental interventions is characterized by the following three points: (i) We can distinguish different modes of experimental interventions according to two standards: the interventional *direction* and the interventional *effect*. (ii) Two interventional directions (vertical/inter-level and horizontal/inter-stage) and two interventional effects (excitatory/positive and inhibitory/negative) can be identified. The vertical or inter-level direction means that an intervention is performed between different levels of organization and the horizontal or inter-stage direction means that an intervention is performed between different stages of a process. (iii) In a series of related experiments, scientists can use multiple interventional modes to *test* given hypotheses and to *explore* novel objects.

Since our study is inspired by the classification of experiments in Craver and Darden (2013), we will begin by summarizing their new mechanistic philosophy and offer a brief characterization of their classification of types of experiments in section 2. Section 3 reinterprets the classification as a framework of interventional modes. Then, we argue that the reinterpretation provides a new framework of the modes of experimental interventions. In section 4, we introduce a new kind of experimental interventions, the inter-stage kind, which Craver and Darden do not mention. Section 3 and 4 jointly argue for the points (i) and (ii). Section 5 takes the PaJaMo experiment on the synthesis of β-galactosidase in *E. coli* to illustrate all the points (i)-(iii). The final section provides a taxonomy of characteristics of experimentation in which the PaJaMo experiment is adequately located.

2. Craver and Darden's classification of types of experiments

Ever since 2000, Craver and Darden jointly develop a mechanism-based and dis-

[2] Woodward has proposed a counterfactual account of the concept of mechanism (Woodward 2002). He argues that components of mechanisms should behave in accord with regularities that are invariant under interventions. On his account, Jacob and Monod's lac operon model and the experimental results will be correctly described and predicted by the notion of modularity of mechanism. Melinda Fagan also has analyzed lac operon model (Fagan 2016). By contrast with Woodward, she argues that the mechanical account with interventions will not always provide an entirely satisfactory account for the case of double preventions or omissions. She proposes a new, complementary mechanistic explanation for that case. However, they focalize on the operon model rather than the PaJaMo experiment in details. The PaJaMo experiment is an important base of construction of the theoretical model.

covery-oriented methodology for biological sciences, especially molecular biology and neuroscience (Machamer, Darden and Craver 2000; Craver and Darden 2001, 2005; Darden and Craver 2002). They majorly analyze reasoning strategies that are used for discovering mechanisms that underling living phenomena. In addition to these analyses, they contribute a long chapter in their 2013 book, *In Search of Mechanisms,* to analyze how experimentation works to help discover mechanisms (Craver and Darden 2013, Ch. 8).

Craver and Darden argue that discoveries of mechanisms are usually made piecemeal via repetitive refinements, which can be guided by interventional experiments. They also analyze processes in which scientists use experimental interventions to test schemas (or models) of mechanisms and then to discover actual mechanisms. In search of a full mechanism, scientists may manipulate some part of a mechanism, intervene in its process, and then observe the changes occur in the termination condition of the mechanism. The observed changes provide a piece of useful evidence or a guide for discerning the entity and activity that are causally relevant to the behavior of the mechanism from that are not. Scientists use the information from manipulations and interventions to infer what could come before or next in the mechanism by "backward chaining" or "forward chaining"[3] (Darden and Craver 2002). A whole picture of the mechanism is thus puzzled out. In their words, scientists use interventional experiments to transform a how-possible constructed schema into a how-actual description of a mechanism (Machamer, Darden and Craver 2000:17; Craver and Darden 2001; 2005:235; Darden and Craver 2002).

In order to provide a full analysis of experimentation, Craver and Darden make a taxonomy of experiments in Chapter 8 of *In Search of Mechanisms*. They distinguish loosely three categories of experiments: those for testing causal relevance, those (interlevel experiments) for testing componential relevance, and those (complex experiments) for asking specific mechanistic questions. The second category is classified into three subkinds: interference experiments that are bottom-up and inhibitory, stimulation experiments that are bottom-up and excitatory, and activation experiments that are top-down and excitatory. The third category is in turn categorized into three subcategories: by-what-activity experiments, by-what-entity experiments, and series of experiment with multiple interventions. They also discuss the famous PaJaMo experiment under the independent title "preparing the experimental system," showing that the experiment also uses multiple interventions.

Craver and Darden emphasize that their goal "is not to offer a systematic taxonomy of experimental types but rather to call attention to the ways that experiments…, to answer specific questions about how a mechanism works." (Craver and Darden 2013:119) However, their work still leaves a strong impression that they are making a taxonomic system of experiments, not only because they use the term "kind" in the context but also because they classify kinds into subkinds. Moreover, they say that interlevel experiments have "the three most common kinds" (p.126) and consider

[3] According to Darden and Craver, backward and forward chaining are reciprocal strategies for discovering mechanisms. When scientists reason about one part of a mechanism on the basis of what is already known in the schematic mechanisms, they can reason from the beginning by forward chaining or from the end by backward chaining. Forward chaining use the experimental results in early stages to reason or conjecture about the information that are likely to be found in later stages; backward chaining is just the reverse (Darden and Craver 2002).

"some alternative kinds of experiments" that fail to fit their intervene-and-detect structure (p.129). All indicates that they are classifying kinds of experiments in the framework of new mechanical philosophy.

Two features in Craver and Darden's taxonomy of experiments are noteworthy. The first feature is that their taxonomy implies a taxonomy of interventional modes, which will be examined in next section. This implication allows us to interpret and treat their taxonomy of experiments as a taxonomy of interventional modes. The second feature is that Carver and Darden pay more attention to experimental tests in the process of discovering a mechanism while say less about experimental investigation, exploration, and discovery. However, experiments in molecular biology often perform many functions other than testing.

Exploratory uses of experimentation have been gotten attention since the end of the 20th century (Burian 1997; Steinle 1997). Exploratory experiments are "driven by the elementary desire to obtain empirical regularities and to find proper concepts" and "typically takes place in those periods of scientific development in which – for what ever reasons – no well-formed theory or even no conceptual framework is available or regarded as reliable." (Steinle 1997:S70) Moreover, a few philosophers of science note that many experiments in classical and molecular biology share the characteristics of exploratory experimentation (Waters 2004; Burian 2007; O'Mallye 2007). Other philosophers such as Kenneth Waters (2008) and Chen (2013) argue that, in classical and molecular genetics, incidental discoveries of novel phenomena in the process of experimenting can be used as investigative tools to discover mechanisms and construct hypotheses or models. For examples, Gregor Mendel's hybridization experiment with peas incidentally discovered the segregation and the independent assortment of hereditary units and led to the discovery of Mendelian mechanism of heredity. Frederick Griffith's experiment with *Pneumococcus* discovered the transformation of bacteria cells and led to a series of discoveries of molecular mechanisms of heredity (Chen 2013). Molecular biologists, M. Hammarlund, E. Jorgensen, and M. Bastianis, learned the crucial guidelines from the unexpected phenomena in their experiment and lead to the discovery of the function of β-spectrin protein in neurons (Waters 2008). In those cases, scientists incidentally discovered the novel phenomena by performing an experiment or a series of organized experiments without the direction of theories, and those discoveries in turn urged them to search for the underlying mechanisms. Experiments that discovered those novel phenomena use interventions and possess an exploratory or investigative characteristic. The previous discussion indicates that reconsidering the exploratory or investigative function of experimental interventions will shed light on the analysis of the PaJaMo experiment and other similar ones in molecular biology.

3. Modes of Experimental Interventions

Craver and Darden (2013) classify the second category of interlevel experiments into three subkinds based on their so-called the invervene-and-detect structure. Interference experiments are bottom-up and inhibitory. Stimulation experiments are bottom-up and excitatory. Activation experiments are top-down and excitatory. In those bottom-up experiments, "one intervenes into a component in a mechanism and detects

changes in the behavior of the mechanism as a whole." (Craver and Darden 2013:125-126) In those top-down experiments, one intervenes on the start conditions to manipulate the phenomenon and detects the behavior of the components in the mechanism. However, we wonder whether or not there are top-down and inhibitory experiments, one intervenes on the start conditions to inactivate or inhibit the phenomenon and detects the behavior of putative components in the mechanism. We think that vaccination experiments are the very kind. In a vaccination experiment, scientists inactivate or reduce the pathogenicity of some kind of pathogenic bacteria by physical and chemical methods or kill them, and then inject the attenuated or killed bacteria vaccine into subjects, and see if target organs of subjects no longer manifest relevant symptoms.

Since all "subkinds" of interlevel experiments share the intervene-and-detect structure, we should interpret the four experimental types as four interventional modes. We view bottom-up and top-down as two different *interventional directions* that are not mutual exclusive, because one may exert different interventional directions into the same mechanism. Similarly, we view excitation and inhibition as two *interventional effects* that are neither mutual exclusive, because an intervention may produce both excitatory effect on one component and inhibitory effects on another component in the same mechanism. Thus, we build up a temporary framework of experimental interventions that has four modes based on the two directions and the two effects: a top-down excitatory, a top-down inhibitory, a bottom-up excitatory, and a bottom-up inhibitory intervention. This is the distinction of interventional modes rather than the taxonomy of experimental types, because different modes may be applied in one and the same experiment.

Consider Julius Axelord's series of experiments that Craver and Darden use to exemplify their third category of series of experiments with multiple interventions. In the series of experiments, Axelrod and his colleagues seek to discover the mechanism for regulating neurotransmitters by conducting multiple interventions at different stage. Craver and Darden reports:

> First, he injected rats with norepinephrine to increase their blood pressure….killing the nerves innervating the eyes and the salivary glands…In a second intervention they then injected the cats with labeled norepinephrine….In a third intervention, they then stimulated the live sympathetic nerve and showed that…transmitter is in fact released from the neurons. In a fourth intervention…they showed that they could prevent the labeled transmitter from being re-sequestered by treating the nerves with cocaine. (Craver and Darden 2013:134-137).

Two features are worth to be pointed out. First, these interventions are operated in both the *top-down* direction on killing the nerves and the *bottom-up* direction on injecting norepinephrine and stimulating the live nerves. They are not mutual exclusive. Second, these interventions produce both an *inhibitory* effect and an *excitatory* effect that are neither mutually exclusive. For example, injecting the neurons with cocaine brings about an inhibitory effect for the nervous system on blocking the reuptake of neurotransmitters, but also produces an *excitatory* effect for endogenous neurotrans-

mitters between two neuron synapses on remaining the positive effect. Interventional effects might be usually opposite, but not be mutually exclusive necessarily. It depends on how initial state or base line being changed by intervention. An excitatory effect should trigger or excite the behavior of the mechanism while an inhibitory effect should eliminate or shut-down the phenomenon. Axelrod's series of experiment just shows that the two interventional directions may be combined with the two interventional effects to form the common framework for the categories of "experiments for testing causal relevance".

4. "Inter-stage" interventions

We now further argue that the framework can be adequately applied to the category of "experiments for testing componential relevance." If our argument is right, then Craver and Darden's distinction between "experiments for testing causal relevance" and "interval experiments for test componential relevance" is unnecessary. Consider vaccination experiments. If some kind of pathogenic bacteria in a vaccination experiment is confirmed as the *etiological cause* of the relevant symptoms and disease, then the interlevel experiments for testing componential relevance can be also interpreted as the experiments for testing causal relevance if we take an integrated view of causality and mechanisms which is developed in Darden (2013:24-26)and Chen (2017:141-143).[4] According to this view, a mechanism has at least five causal aspects: (1) a mechanism as a complete cause, (2) a mechanism piece as a partial cause, (3) a stage in a mechanistic process as a partial or complete cause in a causal chain, (4) an activity in a mechanism as a cause of micro-change in the mechanism, and (5) a disturbance as a cause of an abnormal output of the mechanism (see Fig. 1). These aspects include part-whole relations, for example, entities and activities are parts of mechanism or lower-level mechanisms are parts of higher-level mechanisms; and cause-effect relations, for example, a previous stage is a cause of later stage in a mechanism or making a difference by intervention is a cause of what happens in the later stage.

[4] Darden have articulated the temporal feature of mechanisms. What she argues is that the interfeild relation between Mendelian and molecular biology best characterized as "investigating different, serially integrated, hereditary mechanisms" (Darden 2005). Mechanisms of the two fields operate at different times and are composed of different working entities of different sizes. Our interest in this paper is exploring another aspect of temporal feature, that how a stage of a given mechanism is identified to an etiological factor, and what mode of this intervention will be.

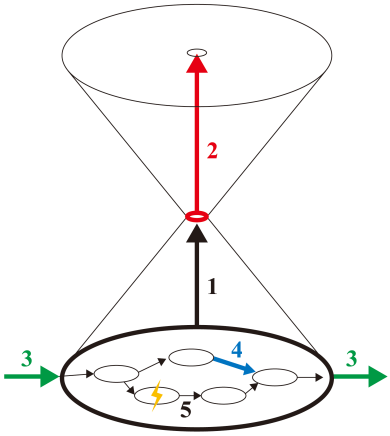

Figure 1. Integrating five causal aspects into a hierarchical structure. Arrow 1, 2, and 4 represent part-whole relations; arrow 3 and lighting bolt with arrow 5 represent cause-effect relations.

This integrated view of mechanism and causality allow us to introduce a kind of "inter-stage" interventions in order to build a more complete framework of experimental interventions. For this purpose, we especially focus on (3), because, since biology is going more and more molecular, even genomic and post-genomic, molecular scientists often need to design and operate interventional experiments to investigate continuous stages of the mechanism involved in embryology, epigenetics and developmental biology. For example, in order to understand how cells having identical genomes develop differentiated and transmit particular characters to the offspring, scientists need to produce various mutations as interventional tools and then to compare of target DNA sequences and the relative gene regulation and expression in a hierarchy of mechanism levels. Their goal is to discover the various stages occurring in a particular order of a mechanism.

That's why we need to take the temporal and etiological factor into our account. In such cases, the causal relevance exists between different stages rather than between different levels. As a consequence, we have "inter-stage" experimental interventions, whose direction is horizontal. By contrast, the direction of the bottom-up and top-down interventions is vertical.

Interventions in the vertical direction occur between two levels, for examples, neuroscientists may put the rat in a maze and record the electrical activity of neurons in the rat hippocampus, and molecular biologists may intervene on one nucleotide sequence that codes some genetic information in organisms and observe the impact in the behavior of a mechanism as a whole. As we have seen in Section 3, vertical or "inter-level" interventions have the "top-down" and the "bottom-up" kinds or modes. Interventions in the horizontal direction occur in different stages in a mechanistic process, for example, molecular biologists may engineer a part of a mechanism at the phase of the initiation of transcription and investigate changes on the later steps of elongation or termination. Particularly the regulatory mechanisms have different working entities serially operating at different times in an extended process. The inter-level kind of interventions can be used to test and investigate any putative part of

some mechanistic model while the inter-stage kind can be used to test and investigate any putative stage of some mechanistic process.

To determine the feature of an entity or activity involved in the mechanism, scientists attempt to *make some difference* at the inputs and see whether such an intervention brings about some corresponding change at the outputs. If the entity or activity plays an excitatory role in the mechanism (such as an excitatory neurotransmitter and promoter), then removing it should induce or in some way prevent the phenomenon. If the entity or activity plays an inhibitory or regulating role in the mechanism (such as an inhibitory neurotransmitter or repressor), then removing it should excite or at any rate change the phenomenon. If, in contrast, the part plays no role in the mechanism, then making a difference of the component should be of no consequence. There are typically two kinds of consequences: excitatory effect and inhibitory effect. We call the consequences that are tending to activate, excite, stimulate the original states are "excitatory effects". Those that are tending to eliminate, shut-down, inhibit the original states are "inhibitory effects". Adding the horizontal modes to the previous four modes, a we have six interventional modes: top-down excitatory, top-down inhibitory, bottom-up excitatory, bottom-up inhibitory, inter-stage excitatory, and inter-stage inhibitory.

In the excitatory kind of inter-level mode, one intervenes on the start level to enhance or activate some part (e.g., injecting norepinephrine or stimulating the live nerves) and observes the reactions on another level. In the inhibitory kind of inter-level mode, one intervenes on the start level to weaken or inhibit some part (e.g., making a mutation on some sequence of genes) and detects the reactions on another level. In the excitatory kind of inter-stage mode, one intervenes to trigger or increase transcription of the regulated gene at the upstream stage (e.g., adding an activator to help polymerase binding the promoter) and see the changes at the downstream stage. In the inhibitory kind of inter-stage mode, one intervenes to inactivate or shut down a part in the upstream stage and assess the changes at the downstream stage of a particular gene (e.g., knocking out a gene in an organism and investigating the effect of gene loss).

Here we extend Craver and Darden's intervene-and-detect structure to a fuller framework of experimental interventions. We distinguish six interventional modes according to three directions and two kinds of effects. Furthermore, we will argue that the six modes can occur in a single experiment or a series of organized experiments for one and the same subject next section. This work not only answers the question about how many modes of experimental interventions used by molecular biologists, but also gives a more comprehensive view to the role of experimentation contributing to acquire new biological knowledge.

Given a new framework of experimental interventions with six modes, we want to analyze how different interventional modes to be used to test hypotheses and to investigate novel phenomena, entities, or objects.

A basic aim of experimentation is to test hypotheses. There are different types of hypotheses to be put into tests, for examples, a causal hypothesis, or a mechanistic model as a whole, or a putative part (an entity or an activity) of a mechanistic model, or a putative stage of a mechanistic model. In order to uncover a complete mechanism underlying a phenomenon, scientists may perform a lot experiments or a series of ex-

periments to test all causal hypotheses related to a mechanistic model and all assumptions of putative parts and stages of the mechanistic model. Thus, we have classification of tested targets (hypotheses) rather than that of experiments. Different targets may be the common goal of one and the same series of experiments.

Consider the second basic aim of experimentation: to investigate or to explore novel objects. There are many different types of objects to be investigated or discovered, for examples, a new significant phenomenon, or a new entity, or a new kind of activity, or a new mechanism. In order to puzzle out and uncover a complete mechanism underlying a discovered novel phenomenon, scientists may need to perform a series of experiments that can investigate all working entities and all relevant kinds of activities. Thus, we have classification of discovered objects rather that of experiments, because a series of experiments may be performed to discover all relevant objects.

Experimental targets and objects are not mutual exclusive, neither are interventional directions and effects. They all may occur in one and the same experiment or a series of experiment for a single subject. A series of experimental interventions may be performed for two experimental aims, use two interventional directions, and acquire two interventional effects. One can exert an intervention into some mechanism and produce excitatory effects on one component and inhibitory effects on another in the same mechanism, depending on whether or not the feature of the intervened entity is essentially excitatory or inhibitory. Interventions may produce novel or unexpected phenomena that are used to test a mechanistic model and discover the mechanism as a whole. All these experimentally interventional modes make important discoveries in biology. The PaJaMo experiment is the best example for illustrating our claim.

5. Experiments with multiple modes of interventions: discovering the synthesis of β-galactosidas

For a long time, historians of science have characterized the contribution of the PaJaMo experiment to the advancement in molecular biology and have argued the question that who should get the credited with the discovery of the repressor model (Morange 1998). Philosophers of biology have been more concern the questions of how the scientists generated and justified the repressor hypotheses and how the related experiments contributed to discovery mechanisms.

Kenneth Schaffner is the first philosopher who analyzed the PaJaMo experiment from the perspective of theory generation. Under the influence of the logical empiricism, he argues that there is a "unitary logic" covering the reasoning of discovery and justification in the generation of the repressor hypotheses (Schaffner 1974a, 1974b, 1993).[5] On his account, one does not need two kinds of generative contexts or reasoning pattern to understand the generation of new theories.

Marcel Weber (2005) criticized Schaffner's claim that the reasoning employed in generation of new theories is the same as that in justification. He argues that the gen-

[5] Logical empiricists distinguish between the "context of discovery" and the "context of justification". According to the traditional view, philosophy of science only concerns the way in which new theories are corroborated or justified while the way in which new theories are constructed or discover is the subject for history, psychology, or sociology of science (Popper 1959).

uine generative reasoning in the PaJaMo experiment is a kind of analogical reasoning. "In my view, the crucial question on which the validity of Schaffner's conclusion turns is the following: Granted that the repressor model follows deductively from the complete results of the PaJaMo experiment plus some background assumptions, does this deductive argument reflect how Jacob and Monod *actually* generated this hypothesis? Monod's own recollections quoted above suggest that this is not the case. Rather, what Monod implies is that the repressor hypothesis was generated by an *argument from analogy*." (Weber 2005:62) Although analogical reasoning cannot be derived from a deductive argument nor be used in logical justification, it still occurs in the generation of new theories. Weber argues that analogical reasoning can be a kind of rational reasoning pattern even though it does not employ any general rules or procedures (Weber 2005: 55-63). In order to support the argument, Weber draws attention to the PaJaMo experiment. However, he analyzes the experiment in the subject of how biologists generate new theories or hypotheses by solving problems. He does not focus on the methodology of the experimentation in details.

Craver and Darden focus on the experimental analyzing. They propose a mechanism-discovering approach to analyze how the PaJaMo experiments contributes to discover new mechanistic schemas (2013). They take the PaJaMo experiment as a searchlight to reveal how series of experiment with multiple interventions contributes to the construction of new mechanistic model.

> This experiment…ushered in an entirely new way of thinking about the mechanisms by which organisms regulate gene expression. Yet it would distort the structure of the experiment to see it an instance of an experiment for testing causal relevance…or as an experiment driven by the goals of identifying components in a mechanism…Rather, the significance of the experiment lies in its ability to test a hypothesis about the active organization of the mechanism, to reveal that mechanism involves the inhibition of an inhibitor. (Craver and Darden 2013:140)

On their account, the PaJaMo experiment is a series of experiments involving multiple interventions. However, their work is providing the taxonomy of experimental types and their methodology is partial to the mechanism-centered approach. Based on their work, we develop a new framework of interventional modes to reexamine the series of PaJaMo experiments. The new framework comprises plural experimental aims and interventional modes. Among them, the inter-stage intervention as one of the interventional modes has not been mentioned by philosophers of biology before. Our goal is to provide a more complete view for generation of new biological theories that goes beyond the older dichotomies: the distinction between justification and discovery and between theory-centered and phenomenon-centered. In what follows, we first introduce the background, unsolved problems, given hypotheses, and how new phenomenon discovered in the PaJaMo experiments in order.

5.1 Background and unsolved problem

Ever since the middle of the twentieth century, molecular biologists studied the

phenomenon of “diauxy” by combining genetic and biochemical approaches. The puzzling phenomenon was that when two food sources (say, glucose and lactose) were given in a microbial culture, the Escherichia coli bacteria (hereinafter to be referred as bacteria) digested one type of food sources (glucose) first , after a latency period, it digested the other type of food sources (lactose). By many experiments, biologist observed that the phenomenon showed two successive growth curves and separated by a period of lag (see Fag. 2).

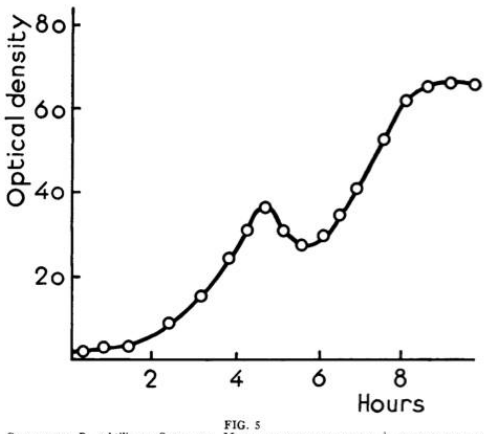

FIG. 5
GROWTH OF *B. subtilis* IN SYNTHETIC MEDIUM WITH D-FRUCTOSE + L-ARABINOSE AS CARBON SOURCE, "DIAUXIC" CURVE (82).

Figure 2. The phenomenon of diauxy was that bacteria would display different digest ability corresponding to specific food resource. It showed two growth curves and separated by a period of lag. Reproduced from Monod, Jacques (1947). “The phenomenon of enzymatic adaptation: And its bearing on problem of genetics and cellular differentiation.” p. 251.

The so-caslled phenomenon of diauxy was first noticed around 1900. In the 1930s and 40s, biologists viewed it a kind of adaptation. They thought that bacteria first produced a kind of enzyme to digest glucose, then, *developed* the ability to produce another kind of enzyme to digest lactose. They called the phenomenon “enzymatic *adaptation*,” because bacteria needed some moments to produce different enzyme. However, this term was dropped for its teleological meaning later.

Another conjecture for the phenomenon was that bacteria contained a general enzyme which could take on various properties for different circumstance changes. When glucose was present, the general enzyme displayed one shape to digest it; when lactose was present, the general enzyme switched another appropriate shape to digest it. The phenomenon of diauxy looked like that lactose stimulated or *induced* bacteria to making the corresponding changes. In the 1950s, biologists renamed the phenomenon “enzyme *induction*” Lactose was called “inducer” because biologists believed that lactose induced bacteria to produce enzymes. However, they did not really understand that what the nature of the “inducibility” was and how the mechanism underling the phenomenon operated.

Today we know that the mechanism underlying the phenomenon of induction is gene regulation, which can be simply described as the following: when both glucose and lactose are present in a microbial culture, bacteria will digest glucose first; when glucose is consumed, the genes of bacteria will begin to synthesize a specific enzymes

(say, β-galactosidase) to digest lactose. In other words, only when lactose is present, the genes synthesize β-galactosidase.

Since 1950s, biologists discovered several main genes involved in the mechanism of gene regulation. The genes can be distinguished to two kinds: structural genes and regulatory genes. There are three structural genes: *lacZ*, *lacY*, and *lacA*. The *lacZ* gene is responsible for encoding the β-galactosidase enzyme, which cleaves lactose into glucose and galactose, both of them are utilized as energy source for the cells. The *lacY* gene is responsible for encoding the enzyme permease, which inserts into cell membranes and transports lactose into the cells. The *lacA* gene is responsible for encoding β-galactoside transacetylase. These three structural genes are expressed only when lactose is present and glucose is absent. The regulatory genes are responsible for encoding two kinds of proteins: an activator called catabolite activation protein (CAP) and a repressor. The CAP normally binds to a specific site on DNA at or near the promoter (which is a region of DNA that initiates the transcription of structural genes) and the repressor binds to the operator (which is a region that regulates the activity of genes). The repressor is encoded by the *lacI* gene. When glucose is present, the repressor will repress the transcription. On the contrary, when glucose is absent and only lactose is present (or an external inducer is added), the repressor will be displaced from operator by inducers, namely repression of the repressor, thus, the *lacZ* and *lacY* genes are *de-repressed* (say, expressed). In this way, the combined effect of two regulators, the activation of the CAP and the repression of the repressor, will make the structural genes to be expressed. So what the unsolved problem here is that how did scientists discover that the enzyme induction could be effected by a mechanism of the repression of a repressor.

5.2 Hypothesis to be tested

The enzyme induction (lactose induces bacteria to produce the enzymes) appears to be a kind of the positive activities of some entity. The repression of the repressor appears to be a kind of the negative activities of some entity. How did an ostensibly positive activity be discovered that was caused by the effect of double negative activities? How did the scientists generate a new mechanistic model for explaining the phenomenon?

In the preparatory stage of the PaJaMo experiment, the scientists only knew that the *lacZ, lacY,* and *lacI* genes played important roles in enzyme induction. But they did not know that how these genes interacted with each other and how these genes organized altogether. They hypothesized the “internal inducer” model that assuming all enzyme induction was caused by a generalized mechanism that was involved in both the synthesis of “inducible” enzymes (i.e., enzymes that were made only in the present of inducers) and the synthesis of “constitutive” enzymes (i.e., enzymes that were made at all times, no matter whether inducers were present or not). In inducible system, the normal *lacI* gene (termed *lacI*+) would produce the inducible enzyme to *inactivate* the internal or endogenous inducer. As a result, the system required an external inducer to activate the *lacZ* and *lacY* genes. In the constitutive system, the mutant *lacI* gene termed (termed *lacI*-) would produce the constitutive enzymes to deactivate the *lacI*+ gene so that allowed the synthesis of the internal inducers. As a

result, no external inducer was needed to activate the *lacZ* and *lacY* genes (Pardee, Jacob, and Monod 1959:174). In addition, they also hypothesized that when the *lacI+* and *lacI-* genes were both present in the cell at the same time, the constitutive system would dominate over the inducible system because of the *lacI-* gene had some stimulating effect on enzyme production.

For these assumptions, the zygote with the *lacZ+* gene and the *lacI+* gene would not produce β-galactosidase unless the external inducer was added because of the *lacI+* gene; the zygote with the *lacZ+* and *the lacI-* would produce β-galactosidase at all times, no matter whether the inducer was present or not, because of the the *lacI-* gene; the zygotes with the *lacZ-* and the *lacI+* genes and the *lacZ-* and the *lacI-* genes wouldn't produce β-galactosidase under any condition because of the *lacZ-* gene. In order to test the internal inducer model, especially the existence of the assuming internal inducers of the constitutive system, the scientists isolated various kinds of normal genes and mutant genes. One of the normal kinds was the *lacZ+* gene that could produce β-galactosidase when met with the *lacI+* and the other normal kind was the *lacI+* gene that could inactivate the internal inducer to keep the system being *inducible* state. One of the mutant kinds was the *lacZ-* gene that lost the capacity to produce β-galactosidase and the other kind was the *lacI-* gene that could produce β-galactosidase constitutively.

5.3 Unexpected phenomena discovered by ensuing experiments

In the stage of testing the internal inducer model, the scientists arranged male bacteria (donor) containing mutant *lacI-* and *lacZ-* genes to mate with female bacteria (recipient) containing normal *lacI+* and *lacZ+* genes, in the absence of inducers. As mentioned above, the scientists predicted that the enzyme synthesis would produce β-galactosidase. In internal inducer model's term, the system would converse from inducible state to constitutive state because of the dominance effect from the male's *lacI-* gene. But to their surprise, the synthesis system did not work. The scientists reasoned that the inducible *lacI+* allele should be dominant over the constitutive *lacI-* allele. The unexpected phenomenon became an anomaly to be investigated. No new model can guide scientist to design new experiments.

In such a situation, the scientists tried to understand the anomaly with the classical genetic reasoning. "This suggests that the dominant allele is the inducible (*i+*). If so, the *i+* should eventually become expressed in mating of type (B) ─ i.e., the zygotes, initially constitutive, should eventually become inducible." (Pardee, Jacob, and Monod 1959:174) In order to investigate the unexpected phenomenon, the scientists performed the experiments in opposite matting direction, that was, arranged male bacterium containing normal *lacI+* and *lacZ+* genes to mate with female bacterium containing mutant *lacI-* and *lacZ-* genes, both in the absent and in the present of inducer. As mentioned above, the scientists predicted that the enzyme synthesis would begin to produce β-galactosidase constitutively. Because when male's *lacZ+* genes entered females' cell, where the mutant *lacI-* gene would produce the assumed internal inducer, the zygote should begin synthesize β-galactosidase and without stopping. But to their surprise again, the synthesis began but *stopped* after about two hours (see the horizontal line in Fig. 3)

Why would the β-galactosidase synthesis interrupt in the circumstances of the presence of assumed internal inducer? Just then, when male's *lacI*+ genes subsequently entered female's cell, the scientists added external inducers, they found that the synthesis was resumed (see the upper and right curve in Fig. 3). How did *lacI*+ genes affect the synthesis to work again? The scientists reasoned, "When inducer added at this stage, enzyme synthesis is resumed, showing that the initially constitutive *z+i+/z-i-* zygotes have not been inactivated, but have become inducible." (Pardee, Jacob, and Monod 1959:175) Such the experimental outcome and explanation were considered to falsify the internal inducer model.

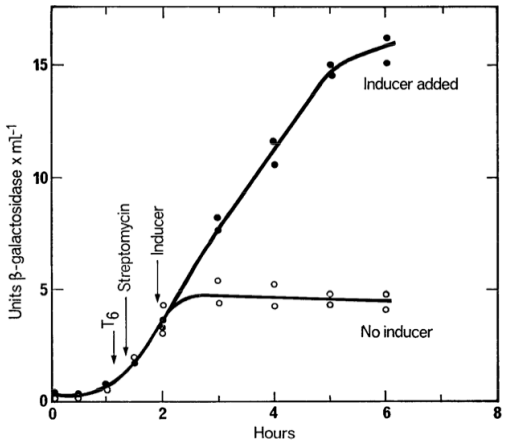

Figure 3. What the scientists observed was that after conjugation, the synthesis began in the absence of inducers, but only for a few hours. After those few hours, the synthesis resumed only in the adding of inducers externally. Reproduced from Pardee, Jacob, and Monod (1959). p. 173.

For a long time, Monod had not completely abandoned the internal inducer model , even attended a seminar which given by Leo Szilard. However, after enough consideration, Monod had started to accept the idea that a kind of the positive activities (induction) could be caused by the effect of double negative activities (the repression of repressors). Then they proposed "the repressor model". The *lacI*+ genes produced the "repressors" (later known were proteins). When no lactose was present in the environment, the repressors would block the synthesis by binding to the operator. When only lactose was present in the environment, the repressors would be inhibited by lactose, thus the genes would be able to synthesize β-galactosidase.

> According to the other, or 'repressor', model the activity of the galactosidase-forming system is inhibited in the wild typify a specific 'repressor' synthesized under the control of the *i*+ gene. The inducer is required only in the wild-type as an antagonist of the repressor. In the constitutive (i-), the repressor is not formed, or is inactive, hence the requirement for an inducer disappears." (Pardee, Jacob, and Monod 1959:176)

Had several new experimental evidences, the scientists had confirmed that the existence of the repressors and convinced that the repression effects had justify the repressor model. The repressor model was not only more empirically adequate than

the internal inducer model but also more simpler than it. Because the repressor model did not require an abstract and nonexistent entity.

5.4 Multiple interventions for different aims and with different modes

The PaJaMo experiment was really a series of interventional experiments for one and the same subject. The experimentation involved multiple interventions for different aims and with different modes. It started with testing a given hypotheses, discovered unexpected phenomena, and then turned to toward an explorative aim without direction of any given hypothesis. After a series of investigation, the scientists provided a new model to solve and explain the novel phenomenon.

In the stage of testing the internal inducer model, the scientists produced the required mutants, to put them in the prepared experimental system, and to entice them to mate with one other. They intervened male bacterium containing the *lacI-* and *lacZ-* genes to mate with female bacterium containing the *lacI+* and *lacZ+*. The experimental result was no synthesis occurred. This is the case of the mode of *vertical* intervention with *inhibitory* effect. In the stage of exploring the new phenomenon, the scientists intervened male bacterium containing the *lacI+* and *lacZ+* genes to inject into female's cell containing the *lacI-* and *lacZ-*. The experimental result was that the synthesis began but stopped later. The immediate synthesis is the result of the mode of *vertical* intervention with *excitatory* effect (because of the *lacZ+* genes). Once the *lacI+* genes also entered the cell, the genes started to produce the repressors. When enough time had passed, the synthesis stopped. This is the result of the mode of *vertical* intervention with *inhibitory* effect. Later, the scientists added the external inducers, then the synthesis re-continued. It is the mode of *horizontal* intervention with *excitatory* effect. Because the scientists engineered the upstream stage of the mechanism of transcription and observed the positive changes of the downstream stage of the mechanism.

The PaJaMo experiment shows us that how multiple interventional modes used in a series of experiments. It also shows us that how interventional experiments used as essential means to realize plural experimental aims.[6] As Morange said, "it (the PaJaMo experiment) represented the final step in the development of a new vision of biology that had been begun in the 1940s and that made the question of the information contained in genes an ordering principle of all life." (1998:159) It brings about the discovery of the mechanism of gene regulation and leads molecular biology entering into a new stage.

6. Categories of Experimentation and the Nature of the PaJaMo Experiment

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[6] With regarding to the investigation of new phenomenon is one of the important experimental aims, we may think of Water's "genetic approach" (Water 2004, 2008). Actually, in our view, the PaJamo experiment generally fits the genetic approach. The scientists *artificially produced mutants* (used required mutants), *gave genetic analyses* (as the scientists said "The suggests that the dominant allele is the inducible (*i+*)…From these observation we may conclude that the constitutive (*i-*) allele is inactive…" (Pardee, Jacob, and Monod 1959:174-175)), and *recombined the mutant to reveal a new biological process* (as the scientists said "…this is precisely the case…is a very strong argument in favor of the repressor model." (Pardee, Jacob, and Monod 1959:174-175)). All these steps leads to the scientific advancement. But Waters did not address the part of the experimental intervention in details.

For a long period of time, people believe that experimentation has only a single aim and function, i.e., testing theories. Since the end of the 20th century, the exploratory aim and function of experimentation has been revealed by some philosophers of science (Burian 1997; Steinle 1997) and gotten much attention (Burian 2007; Elliot 2007; Franklin 2005; O'Malley 2007; Steinle 2002; Waters 2004, 2007). Steinle (1997, 2002)'s distinction between theory-driven experimentation and exploratory experimentation has become a standard frame of categorizing experimentation (Franklin 2005: 888-889; O'Malley 2007: 339; Burian 2007: 286-288). However, these philosophers also emphasize that the distinction between theory-driven and exploratory experimentation does not mark a sharp division and the latter is not free of theory (See Waters 2007: 277-279).[7] Waters further notes the difference between being theory-directed and being theory-informed and the distinction between exploratory and theory-driven experimentation is made by the ways in which an experiment depends on theory (2007: 277). Nevertheless, these philosophers agree the two distinctive categories of experimentation, although not sharp, largely works for methodological analyses. However, we wonder whether or not there would be an experiment or a series of organized experiments which was used to both test hypotheses and explore novel things. If there is one, then what category we should classify it into? The experiment might test a hypothesis, falsify it, find anomalous phenomena, and then enter into an unknown field and become exploratory. Thus, we should say that the experiment is both theory-driven and exploratory. According to the previous discussion, we think that the PaJaMo experiment discussed in the previous section is the just one. As a consequence, this issues a challenge to the two basic categories of theory-driven and exploratory experimentation.

Elliot develops a taxonomy of exploratory experiments by discerning different kinds according to the three relatively independent dimensions: aims of experimental activity, role of theory in the activity, and methods or strategies for varying parameters (2007: 324). According to his taxonomy, "testing a hypothesis" is neither an aim of nor plays a role in an exploratory experiment. The aims of exploratory experiments include (1) "identifying regularities and developing new concepts," (2) "isolating or manipulating particular entities or phenomena," (3) "developing experimental techniques, instrumentation, or simulations," and (4) "resolving anomalies." The PaJaMo experiment explicitly realized aim 1 and 4. In order to resolve the classifying problem, one may simply add a third hybrid category of experimentation to the dichotomous categories. As a consequence, the PaJaMo experiment should be classified to

[7] All Burian (2007), Elliot (2007), and O'Malley (2007) emphasize this point. Burian points that there are a sharp methodological divisions between advocates of "hypothesis driven science" and advocates of "data-driven science". However, he emphasizes "[I]t is important to reduce the sharpness of this supposed dichotomy." (2007: 286-287) Elliot (2007) claims that theory plays a minimal role relative to other forms of experimentation and characterizes a few roles of theory in exploratory experimentation (2007: 324). O'Malley examines the interaction between exploratory and theory-driven experimentation within the context of an exploratory program of research.

the third hybrid category.[8] However, this resolution brings the new problem of the proliferation of varieties of hybrid experiments: for examples, experiments for both aim of testing and aim of manipulating particular entities, experiments for both aim of testing and aim of developing techniques, and so on. The point is to categorize experimentation according to some relatively independent dimensions or criteria as those Elliot (2007) has provided.

At this point, let us discuss Elliot's three independent dimensions. First, we can simply add the aim of testing hypotheses, model, and theories to the dimension of "aims of experimental activities." Second, we take Waters' distinction between "theory-directed" and "theory-informed" as two sub-dimensions of "role of theory in experimentation." In order to offer a more full taxonomy of the second dimension, we want to add a third sub-dimension "theory-free".[9] As for Elliot's third dimension of "methods or strategies for varying parameters, we want to introduce the two sub-dimensions of "interventional" and "non-interventional" to match up the topic of this paper, in which we draw a taxonomy of interventional modes from Craver and Darden's taxonomy of experiments. To sum up the previous discussion, we build the following table:

Dimensions of experimentation	Varying Characteristics of Experimentation with the Dimensions
Aims of Experimental Activities	Testing hypotheses Identifying regularties Developing new concepts Isolating or manipulating entities Developing techniques and instrumentation Simulating Resolving Anomalies
Role of Theory in Experimentation	Theory-directed: Testing hypotheses; Identifying regularties; Developing new concepts, etc. Theory-informed: Providing background information; Serving as a starting pont or foil; New theory being constituted by exploratory projects, etc. Theory-free

[8] The other resolution is the appealing to Waters' distinction between experiments and programs of investigative research which combines explanatory reasoning with investigatory strategies (Waters 2004, 2007, 2008). According to this resolution, the PaJaMo experiment should be treated as a part of a program of investigative research for the regulatory mechanism of genes. However, our aim in this paper is only to analyze the PaJaMo experiment.

[9] Whether or not there are theory-free experiments depends on our interpretation or theory of the term "theory". Here we take a narrower interpretation of "theory" and set up the sub-dimension "theory-free".

Methods or Strategies of Varying Parameters	Interventional: [1] Interventional direction: Bottom-up or Top-down or Inter-stage [2] Interventional effect: Excitatory or Inhitatoty Non-interventional

Table 1: A taxonomy of characteristics of experimentation according to three relatively dimensions

We believe that we can provide a more complete analysis of interventional experiments in molecular biology according to the framework of three experimental dimensions presented in the Table 1.

7. Concluding remarks

We have argued that multiple experimental interventions are frequently used in biological practice. We have provided a taxonomy of modes of experimental interventions that are developed from Craver and Darden's taxonomy of experiments. The taxonomy of interventional modes is built according the three directions (top-down, bottom-up, and inter-stage) and two effects (excitatory and inhibitory). We reexamine the famous PaJaMo experiment (a series of experiments for a single subject) to illustrate the new taxonomic framework. We find that scientists pursue both aims of testing hypotheses and investigating new phenomena. This motivate us to further consider the possibility that a series of experiments is performed to realize the different aims of experimentation by using different strategies or methods. As a result, we provide a new taxonomy of characteristics of experimentation in which the molecular biological practice is adequately analyzed in the light of multiple aims and interventions.

References

Bechtel, William and Adele Abrahamsen (2005). "Explanation: A Mechanist Alternative." *Studies in History and Philosophy of Biological and Biomedical Sciences* 36:421-441.

Burian, Richard M. (1997). "Exploratory Experimentation and the Role of Histochemical Techniques in the Work of Jean Brachet, 1938-1952." *History and Philosophy of the Life Science* 19:27-45.

Burian, Richard M. (2007). "On microRNA and the Need for Exploratory Experimentation in Post-Genomic Molecular Biology." *History and Philosophy of the Life Sciences* 26:285-311.

Chen, Ruey-Lin (2013). "Experimental Discovery, Data Models, and Mechanisms in Biology: An Example from Mendel's Work." In Chao, Hsiang-Ke, Szu-Ting Chen, and Roberta L. Millstein (eds.). *Mechanism and Causality in Biology and Economics*. Dordrecht: Springer Press.

Chen, Ruey-Lin (2017). "Mechanisms, Capacities, and Nomological Machines: Inte-

grating Cartwright's account of nomological machines and Machamer, Darden and Craver's account of mechanisms." In Chao, Hsiang-Ke, Szu-Ting Chen, and Julian Reiss (eds.). *Philosophy of Science in Practice: Nancy Cartwright and the Nature of Scientific Reasoning*. New York: Springer Press.

Cohen, G. N. and Jacques Monod (1957). "Bacterial Permeases." In Andre Lwoff and Agnes Ullmann (eds.) *Selected Papers in Molecular Biology by Jacques Monod*. Academic Press Inc.

Craver, Carl F. and Lindley Darden (2001). "Discovering Mechanisms in Neurobiology: The case of Spatial Memory." In Machamer, Peter, R. Grush, and P. McLaughlin (eds.) *Theory and Method in the Neuroscience*. Pittsburgh: University of Pittsburgh Press. Reprinted in Darden 2006, ch. 2.

Craver, Carl F. (2002). "Interlevel Experiments, Multilevel Mechanisms in the Neuroscience of Memory." *Philosophy of Science* (Supplement) 69:S83-S97.

Craver, Carl F. and Lindley Darden (2005). "Introduction: Mechanisms Then and Now." In Craver, Carl F. and Lindley Darden (eds.) *Studies in History and Philosophy of Biological and Biomedical Science*. Special Issue, "Mechanisms in Biology" 36:233-244.

Craver, Carl F. (2007). *Explaining the Brain: Mechanisms and the Mosaic Unity of Neuroscience*. Oxford: Clarendon Press.

Craver, Carl F. (2008). "Axelrod, Julius" In Noretta Koertge (ed.) *New Dictionary of Scientific Biography*. Detroit, MI: Charles Scribner's Sons/Thomson Gale.

Craver, Carl F. and Lindley Darden (2013). *In Search of Mechanisms: Discoveries across the Life Sciences*. Chicago: The University of Chicago Press.

Darden, Lindley (1991). *Theory Change in Science: Strategies from Mendelian Genetics*. Oxford: Oxford University Press.

Darden, Lindley (2006). *Reasoning in Biological Discoveries: Essay on Mechanisms, Interfield Relations, and Anomaly Resolution*. Cambridge: Cambridge University Press.

Darden, Lindley (2013). "Mechanisms versus Causes in Biology and Medicine." In Chao, Hsiang-Ke, Szu-Ting Chen, and Roberta L. Millstein (eds.). *Mechanism and Causality in Biology and Economics*. Dordrecht: Springer Press.

Darden, Lindley and Carl.F. Craver (2002). "Strategies in the Interfield Discovery of the Mechanism of Protein Synthesis." *Studies in History and Philosophy of Biological and Biomedical Sciences* 33:1-28. Corrected and reprinted in Darden 2006, ch. 3.

Elliott, Kevin C. (2007). "Varieties of Exploratory Experimentation in Nanotoxicology." *History and Philosophy of the Life Sciences* 29 (3): 313-336.

Fangan, Melinda B. (2016). "Interventionist Omissions: A Critical Case Study of Mechanistic Explanation in Biology." *Philosophy of Science* 83:1082-1097.
Glennan, Stuart S. (1996). "Mechanisms and the Nature of Causation." *Erkenntnis* 44:49-71.

Franklin, Laura R. (2005). "Exploratory Experiments." *Philosophy of Science 72*: 888-899.

Glennan, Stuart S. (2002). "Rethinking Mechanistic Explanation." *Philosophy of Science (Supplement)* 69:S342-S353.

Hogness, David S., Melvin Cohn and Jacques Monod (1955). "Studies on the Induced

Synthesis of β-galactosidase in Escherichia Coli: The Kinetics and Mechanims of Sulfur Incorporation." In Andre Lwoff and Agnes Ullmann (eds.) *Selected Papers in Molecular Biology by Jacques Monod*. Academic Press Inc.

Jacob, Francois and Jacqes Monod (1961). "Genetic Regulatory Mechanisms in the Synthesis of Protein." *Journal of Molecular Biology* 3:318-356.

Judson, Horace F. (1996). *The Eighth Day of Creation: The Makers of the Revolution in Biology*. Expanded Edition. Cold Spring Harbor., NY: Cold Spring Harbor Laboratory Press.

Machamer, Peter, Lindley Darden, and Carl F. Craver (2000). "Thinking About Mechanisms." *Philosophy of Science* 67:1-25.

Morange, Michel (1998). *A History of Molecular Biology*. Cambridge, Mass: Havard University Press.

Monod, Jacques (1947). "The Phenomenon of Enzymatic and its adaptation: And its Bearing on Problem of Genetics and Cellular Differentiation." In Andre Lwoff and Agnes Ullmann (eds.) *Selected Papers in Molecular Biology by Jacques Monod*. Academic Press Inc.

Monod, Jacques (1950). "Adaptation, Mutation and Segreation in the Formation of Bacterial Enzymes." In Andre Lwoff and Agnes Ullmann (eds.) *Selected Papers in Molecular Biology by Jacques Monod*. Academic Press Inc.

Monod, Jacques (1956). "Remarks on the Mechanism of Enzyme Induction." In Andre Lwoff and Agnes Ullmann (eds.) *Selected Papers in Molecular Biology by Jacques Monod*. Academic Press Inc.

Monod, Jacques (1958). "An Outline of Enzyme Induction." *Recueil* 77(6):569-585.

Monod, Jacques ([1965] 1977). "From Enzymatic Adaptation to Allosteric Transition." Reprinted in *Nobel Lectures in Molecular Biology: 1933-1975*, pp. 259-82. New York: Elsevier.

O'Malley, Maureen (2007). "Exploratory Experimentation and Scientific Practice: Metagenomics and the Proteorhodopsin Case." *History and Philosophy of Life Science* 29:335-358.

Pardee, Arthur B., François Jacob and Jacques Monod (1958). "Sur l'expression et le rôle des allèles «inductible» et «constitutif» dans la synthèse de la β-galactosidase chez des zygotes d'Escherichia Coli." [The role of the inducible alleles and the constitutive alleles in the synthesis of beta-galactosidase in zygotes of Escherichia cloi.] C. R. Hebd Seances Acad. Sci. 246:3125-8.

Pardee, Arthur B., François Jacob and Jacques Monod (1959). "The Genetic Control and Cytoplasmic Expression of 'Inducibility' in the Synthesis of β-galactosidase by E. Coli." In Andre Lwoff and Agnes Ullmann (eds.) *Selected Papers in Molecular Biology by Jacques Monod*. Academic Press Inc.

Pardee, Arthur (1979). "The PaJaMa Experiment." In Lwoff, Andre and Agnes Ullmann (eds.) *Origins of Molecular Biology: A Tribute to Jacque Monod*, pp. 109-116. New York: Academic Press.

Popper, Karl, R. (1959). *The Logic of Scientific Discovery*. London: Hutchinson Edu cation.

Schaffner, Kenneth (1974a). "Logical of Discovery and Justification in Regulatory Genetics." *Studies in History and Philosophy of Science* 4:349-385.

Schaffner, Kenneth (1974b). "The Peripherality of Reductionism in the Development

of Molecular Biology." *Journal for the History of Biology* 7:111-139.
Schaffner, Kenneth (1993). *Discovery and Explanation in Biology and Medicine*. Chicago, IL: University of Chicago Press.
Steinle, Friedrich (1997). "Entering New Fields: Exploratory Uses of Experimentation." *Philosophy of Science* (Proceedings) 64:S65-S74.
Steinle, Friedrich (2002). "Experiments in History and Philosophy of Scence." *Per spectives on Science* 10: 408-432.
Waters, C. Kenneth (2004). "What was Classical Genetics?" *Studies in History and Philosophy of Science* 35:783-809.
Waters, C. Kenneth (2007). "Causes that Make a Difference." *Journal of Philosophy* 104 (11): 551-579.
Waters, C. Kenneth (2008). "Beyond Theoretical Reduction and Layer-Cake Antireduction: How DNA Retooled Genetics and Transformed Biological Practice." In Michael Ruse (ed.) *The Oxford Handbook of Philosophy of Biology*. Oxford: Oxford University Press.
Weber, Marcel (2005). *Philosophy of Experimental Biology*. New York: Cambridge University Press.
Woodward, James (2002). "What Is a Mechanism? A Counterfactual Account." *Philosophy of Science (Supplement)* 69:S366-S377.
Woodward, James (2003). *Making Thing Happen: A Theory of Causal Explanation*. Oxford: Oxford University Press.
Woodward, James (2006). "Sensitive and Insensitive Causation." *Philosophical Review* 115:1-50.