An Experiment-based Methodology for Classical Genetics and Molecular Biology

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Abstract

This paper proposes an experiment-based methodology for both classical genetics and molecular biology by integrating Lindley Darden’s mechanism-centered approach and C. Kenneth Waters’ phenomenon-centered approach. We argue that the methodology based on experiments offers a satisfactory account of the development of the two biological disciplines. The methodology considers discovery of new mechanisms, investigation of new phenomena, and construction of new theories together, in which experiments play a central role. Experimentation connects the three type of conduct, which work as both ends and means, occurring in a circular way and constituting an overall process of scientific practice from classical genetics to molecular biology.

Key words: classical genetics, molecular biology, Lindley Darden, C. Kenneth Waters, reductionism, mechanism, discovery, experimentation

1. Introduction

This paper addresses a set of methodological questions about classical genetics and molecular biology: What is the methodology for classical genetics? What is the methodology for molecular biology? What is the methodology or the methodological relationship for the turning from classical genetics to molecular biology? We propose an experiment-based methodology to answer the three questions. Ever since the era of logical empiricism, philosophers of science had invoked the general explanation centered (or hypothetical-deductive) methodology to answer the first two questions and theory reductionism to the third question. Then, theory anti-reductionism emerged to resist reductionism regarding the third question, but kept consistent with reductionism regarding the first two questions. However, all explanation-centered methodology, reductionism, and antireductionism seem to neglect the crucial role of experiments play in both disciplines. In the beginning of the twentieth-first century, a

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few of philosophers of science have begun to search for alternative, practice-oriented approaches. Our proposal is one among them. In order to justify our proposal, we start by reviewing this history of methodological theories. We will focus on the methodological relationship question, because it covers the first two ones.

It has been over fifty years since philosophers of science started examining the problem of what is the adequate theoretical relationship between classical genetics and molecular biology. This relationship presents a methodological framework for biologists to treat the two disciplines. Reductionists claim that classical genetics should be and was indeed reduced to molecular biology, while antireductionists reject this claim. Two distinguished American philosophers of science, Lindley Darden and C. Kenneth Waters, propose two different but similar new approaches to the issue (Darden 2005; Waters 2004, 2008). They both believe that scientific practices in classical genetics and molecular biology have been largely neglected by the two camps. However, their approaches are different in style and in direction, since they are concerned about different aspects of practices in the two fields.

This paper compares the two philosophers’ approaches and develops an integrative account based on their respective insights, thus proposing an experiment-based methodology. Our arguments are developed along the following structure. Section 2 starts with the old debate of reductionism and antireductionism. Section 3 examines the role of scientific discoveries in the advancement from classical genetics to molecular biology. According to our analysis, Darden emphasizes discovery of mechanisms, while Waters focuses on an investigation of new phenomena in both disciplines. As a consequence, Darden has developed a methodology centered on the discovery of mechanisms and reasoning about mechanisms, while Waters has also proposed another methodology centered on the discovery of phenomena with explanatory and investigative reasoning. Section 4 introduces and examines the two methodologies with different centers for the current biological disciplines. We argue that their approaches have shifted the relationship problem between classical genetics and molecular biology to the problem of whether there is a common methodology for both disciplines. Section 5 presents that neither Darden’s nor Waters’ approaches can singly provide a satisfactory account. A new account that integrates their respective insights is better. In order to do this, we should consider the discovery of new mechanisms, and the investigation of new phenomena, and the construction of new theories with attendant models together. All three types of conducts work as both end and means in which experiments play a central role. They occur in a circular way, constituting an overall process of scientific practices from classical genetics to molecular biology. A methodology taking experiments as the basis is thus established, because the discovery of mechanisms, the investigation of phenomena, and the construction of theories in both fields deeply depend on experiments. However, in order to reduce the argumentative complexity in this paper, we simply include the construction of
theories without any detailed analysis and focus on the discovery of mechanisms and the investigation of new phenomena. Thus, we offer a united answer to the three methodological questions.

2. The old debate over the reduction problem

Ever since the era of logical empiricism, the reductionism of scientific theories has always been the mainstream view in the philosophy of science. Ernest Nagel (1961) and Carl G. Hempel (1966) develop a standard view or general theory of reductionism, claiming that a theory can be justified by being reduced to a more fundamental theory. The reductive relation between two theories is defined by the deductive relation between the reduced theory and the reducing theory - that is, if a theory can deduce the other theory, then the former is the reducing theory and the latter the reduced theory. Moreover, according to the deductive-nomological model of explanation, explaining a phenomenon is deducing the phenomenon from a set of theoretical generalizations, while explaining a lower-level theory is deducing that theory from a higher-level theory (Nagel 1961, Hempel 1966). This central theme of reductionism indicates a normative methodology that is especially suitable to the following situations: (1) Using underlying generalizations to explain apparent generalizations; (2) Using micro entities, micro structures, and micro activities to explain macro entities and the phenomena that those macro entities produce under interaction; (3) Using more universal generalizations to explain relatively particular generalizations. Philosophers of science endorsing this view generally claim that scientists should make the progress via reducing an old theory to a new and more fundamental one.

The standard view of reductionism is supposed to be applied to many important theory pairs, including Galileo’s theory of free falls and Newtonian mechanics, Kepler’s laws of planets and Newtonian laws of gravitation, Newtonian mechanics and Einstein’s theory of relativity, thermodynamics and statistical mechanics, chemistry and quantum mechanics, classical genetics and molecular biology, individual psychology and neurobiology or brain science, and many others in the history of science. The question of whether the reductive relationship between classical genetics and molecular biology can be justified or not is the central concern of philosophers who are interested in biology. Philosophers of science have debated over how to understand the adequate relationship between classical genetics and molecular biology for over fifty years. Based on Ernest Nagel’s general theory of reduction, reductionists argue that molecular biology is a fundamental theory and classical genetics could and should be explained by (that is, be deduced from or be reduced to) the fundamental theory. One can find or establish bridge rules that connect key terms in classical genetics (for example, “gene”) to correspondent terms in molecular biology (for example, “a segment of DNA”). Thus, one can deduce the central positions in classical
genetics from the correspondent propositions in molecular biology via those bridge rules (Schaffner 1969, 1993; Waters 1990).

Antireductionists argue that the actual relationship between two theories is extremely complicated. No bridgeable connections between the key terms in any two theories can be found or established. Phenotypic differences among organisms can be fully explained singly at the level of cells, like classical geneticists such as Thomas Hunt Morgan and his team who worked at explaining hereditary phenomena. Moreover, the meaning of “gene” in classical genetics is defined by the loci of genes in chromosomes and by their functions to output heredity, mutation, and recombination. This meaning is quite different from that in molecular biology, in which a gene is identified with “an encoded framework for producing a specific chain of polypeptides.” As a consequence, the assumed deduction is not really available. (Kitcher 1984; Rosenberg 1985) For antireductionists, expecting biological phenomena at many different levels to be explained in terms of molecular biology is a truly unrealistic idea.

Which is more adequate, reductionism, or antireductionism, or some other alternative?

3. Two alternatives to the methodology problem: the mechanism-centered and the phenomenon-centered approaches

Two American philosophers of science, Lindley Darden and C. Kenneth Waters, attempt to go beyond the old debate, proposing two different but similar new approaches to the relationship problem. They both believe that scientific practices have been largely ignored by the camps of both reductionists and antireductionists, arguing that we would not have a satisfactory account of the issue unless we carefully examine the practices in classical genetics and in molecular biology. For them, the methodological relationship between the two fields is more practice-oriented rather than purely theoretical.

Darden notes that both camps in the old debate of reductionism versus antireductionism neglect the practices of biologists from different fields, including classical genetics, cytology, and molecular biology, as she says that “[· · ·] we see that Mendelian genetics has not been reduced to molecular biology nor replaced by it.” (Darden 2005: 367) On the one hand, she shares the view of antireductionists who see that the appropriate explanation of phenotypic differences can be achieved singly at the level of cytology without molecular biology. On the other hand, she agrees with reductionists’ point (for example, Waters 1990) that molecular biologists have extended the explanation of crossover phenomena via providing a complicated mechanism at the level of molecular biology. For Darden, however, both camps do not grasp the most important fact: What we should consider is not only classical genetics and molecular biology, but also other disciplines such as biochemistry, cytology, embryology, and
even evolutionary theories. All disciplines contribute to the explanation of hereditary phenomena via discoveries of mechanisms at different levels and in different contexts and fields. Cytologists discovered the mechanisms of cell mitosis and meiosis; classical geneticists used those mechanisms to explain the ratios of Mendelian laws and other ratios from Morgan’s experiments on fruit flies (*drosophila melanogaster*); biochemistry discovered the energy sources of cell activities; molecular biology discovered the structure of hereditary materials (say, DNA) and then the molecular mechanism of DNA reproduction, that of DNA mutation, and that of protein synthesis.

Darden obviously proposes a mechanism-centered approach to the old issue. To account for the development from classical genetics to molecular biology, one has to study the ways by which biologists can discover different, serially-integrated mechanisms underlying the related phenomena. She argues that moving to lower levels in the size of objects can make progress in some cases and cannot in other cases. Therefore, theory reductive methodology is not the only way from classical genetics to molecular biology. Scientific advancement in biology in the 20th century was nurtured by discovering new mechanisms and integrating them into a temporal series rather than by reducing the theories at the level of cell to the theories at the level of molecule.

Although Waters (1990) criticizes the antireductionists’ consensus at an earlier time, he has developed a new view on the issue in his later papers (Waters 2004, 2008). Like Darden, Waters thinks that both reductionists and antireductionists have neglected scientific practices. Furthermore, he questions the adequateness of the explanation-centered approach commonly adopted by reductionists and antireductionists, as well as the mechanism-centered approach. He argues that scientists (geneticists and molecular biologists) are usually not interested in explaining the principles of classical genetics in terms of physicochemical principles of molecular biology. Rather, scientists are more earnest in investigating new phenomena by means of explanatory theories, because the investigation of new phenomena is the very end while explanatory theories are only the means. For Waters, philosophers would get it wrong if they assume the construction of explanatory theories is the end of scientific research (in particular, for biology in the 20th century). Scientists use explanatory reasoning to uncover possibilities of new phenomena and then design experiments to investigate them. If there are novel results that are not predicted by theoretical explanations, then they would perform investigative reasoning to judge whether they are novel phenomena. Waters argues that investigative practices by means of combining investigative reasoning and explanatory reasoning helped realize the advancement from classical genetics to molecular biology. Therefore, Waters believes that theoretical reductionists have misplaced the peripheral thing in the center. Let us call the methodology that Waters reconstructs from classical genetics and molecular biology the phenomenon-centered approach.
Although both Darden and Waters criticize reductionism and antireductionism, their new approaches seem to conflict with each other. According to Waters’ view, the search of mechanisms is nothing but the construction of explanatory theories. Darden regards the search of mechanisms as the focus of scientific practices. Is the conflict apparent or substantive? Before addressing this question, let us introduce their approaches in detail.

The new mechanistic philosophers start with answering two questions: What are mechanisms? How do we characterize and understand them? Biologists usually use this term, but seldom interpret it. Darden and her collaborators, Peter Machamer and Carl Craver, characterize (or define) “mechanism” in a new, clear, simple, and concise way.

Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions. (Machamer, Darden and Craver 2000: 3; hereafter MDC)

This characterization is generally known as the MDC mechanism. Machamer, Darden and Craver (hereafter, MDC) think that activities cannot be reduced to entities and changes of properties, and vice versa. This conception of mechanisms thus claims a dualism: both substances and processes exist in their own right (Machamer 2004: 27). To give a detailed account of the main components of mechanisms, activities in a mechanism may pass through a number of stages and thus produce regular phenomena. As MDC say:

Activities are the producers of change. Entities are the things that engaged in activities. Activities usually require that entities have specific types of properties. · · · The organization of these entities and activities determines the ways in which they produce the phenomenon. · · · Mechanisms are regular in that they work always or for the most part in the same way under the same conditions. The regularity is exhibited in the typical way that the mechanism runs from beginning to end; what makes it regular is the productive continuity between stages. (MDC 2000: 3)

From this quotation above, we can identify four central features of mechanisms: organization, production, productive continuity, and regularity. In addition, MDC mechanisms are often embedded in nested hierarchical structures. As MDC state:

Mechanisms occur in nested hierarchies and the descriptions of mechanisms in neurobiology and molecular biology are frequently multi-level. The lev-

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1 See Chen (2017) for an analysis in greater details. We borrow three of the four concepts – organization, productive continuity, and regularity – from Skipper and Millstein’s work (2005).
els in these hierarchies should be thought of as part-whole hierarchies with the additional restriction that lower level entities, properties, and activities are components in mechanisms that produce higher level phenomena. (MDC 2000: 13)

For example, the mechanism of heredity may be described as the transmission of traits at the level of individual organisms, as the activities of chromosomes at the level of cells, and as the activities of DNA, RNA, and protein at the molecular level. Mechanisms at different levels are discovered by way of scientific research from different fields and they may be integrated into a nested hierarchy of mechanisms in a temporal order. In order to achieve the integration, investigations that focus on different working entities in size from different fields are necessary.

The integration of mechanisms sometimes involves two fields within one level (e.g., the mechanism of protein synthesis involves biochemistry and molecular biology at the molecular level) and sometimes involves three fields (inter-field) and multiple levels, in which multiple submechanisms are discovered in a sequential or temporal series (e.g., the mechanism of heredity). Since many submechanisms in different fields or at different levels have been discovered, scientists might search for a mechanism scaffold that connects those separate submechanisms in order to offer an overall explanation of all related phenomena. As biologists successfully build a mechanism scaffold, the integrated mechanism will explain more than do original mechanisms in a single field or at a single level. As the new mechanism is composed of submechanisms in different fields or at different levels, it becomes an “upgraded” mechanism that covers more fields or more levels. Finally, one may say that the integration of a new, inter-field, and upgraded-level mechanism is a new discovery (in the sense of theory). Sometimes, philosophers interpret the kinds of scaffolds as theories - for examples, the basic theory of classical genetics or the basic theory of molecular biology. However, we should see those theories as only byproducts of discoveries of new mechanisms.2

Like the mechanism-centered approach, Waters presents that the progress in genetics was not made by reducing the basic theory of classical genetics to the basic theory of molecular biology, because “it focuses on something that is peripheral to advancing scientific research.” (Waters 2008: 249) Moreover, “geneticists are not interested in explaining the principles of classical genetics in terms of physicochemical

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2 Regarding the relationship between “theory” and “mechanism schemata,” MDC say: “Neurobiologists and molecular biologists sometimes use the term ‘theory’ to refer to hierarchically organized mechanism schemata of variable, though generally less than universal, scope. Mechanism schemata, as well as descriptions of particular mechanisms, play many of roles attributed to theories. They are used to describe, predict, and explain phenomena, to design experiments, and to interpret experimental results.” (MDC 2000: 16–17)
principles of molecular biology.” (Waters 2008: 249) Thus, Waters thinks that the antireductionists, as well as the mechanism-centered approach, do not get the adequate methodological relationship, because of its explanation-centered orientation (Waters 2008: 244–248). The progress of biology, Waters argues, has been made by taking the investigation of new phenomena as the central goal rather than by moving toward an explanatory expansion.

Waters calls dominant antireductionism in this debate layer-cake antireductionism. It makes two basic claims: (1) genes cannot be conceived at the molecular level; (2) classical genetics offers objectively better explanations of certain transmission phenomena than any molecular-level explanation could ever provide. Waters argues against the two claims. First, “the differences used by classical geneticists to explain inheritance patterns have been routinely identified at the molecular level by contemporary geneticists.” (Waters 2008: 247) Second, the explanation of the dominance phenomenon provided by contemporary molecular theory is deeper than is the explanation by classical genetics.

What is wrong with both layer-cake antireductionism and reductionism? Waters argues that both reductionism and antireductionism use a common theory-dominated or theory-driven approach, because both camps believe that geneticists always make every endeavor to explain hereditary phenomena and to expand the range that has been explained. The difference is that reductionists hold that the basic theory of molecular biology offers a foundation for the basic theory of classical genetics, while antireductionists insist that the latter can explain some phenomena at the level of cytology better than the former can. However, both camps do believe that developing a central theory is the end of scientific research and explaining phenomena is the means to achieve this ultimate end. Waters describes this common theory-dominant approach:

Typically, it is taken for granted that the developments were theoretical. According to the popular view, which is frequently advanced by scientists and science writers, a new fundamental theory of molecular biology, constructed in the decades following Watson and Crick’s discovery, transformed biology by providing a basis for explaining a wide variety of phenomena. (Waters 2008: 238–239)

Waters believes that it is time to move beyond the dichotomy of reductionism and antireductionism. He suggests that philosophical attention should be shifted from theory to practice. The first step is to remove theory bias, as he says:

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3 In a note, Waters implicitly ascribes some literature from mechanism-centered philosophers (e.g., Wimsatt, Darden and Maull) to the view of antireductionism (Waters 2008: 259, note 5).
Theory bias is ubiquitous, not just among theoretical reductionists and layer cake antireductionists, but among philosophers of science in general. Removing this bias will enable us to look beyond the layer-cake image and see what Watson and Crick’s discovery did for genetics and how the resulting development in genetics transformed scientific practice throughout much of biology. (Waters 2008: 240)

To show the practical turn, Waters examines the classical geneticist Sturtevant’s investigation of the process of crossover (Sturtevant and Beadle 1939), arguing that this discovery is so important to classical genetics, because a new basic phenomenon (synaptic attraction between chromosomes during the process of meiosis) was discovered. Although the new phenomena are explained by using transmission theory, we cannot see those explanations as Sturtevant’s end of experiments.

The phenomenon of crossover between two homologous chromosomes is frequent in the process of cell meiosis. Waters argues that Sturtevant conducted many breeding experiments on this phenomenon, but he did not design those experiments according to an explanatory theory or end. Instead, he wanted to know more about this phenomenon and its variants. Explaining this phenomenon is not the end of his experiments, because the basic explanatory pattern the classical geneticists take remains the same. In order to investigate what factors cause the dramatic decrease in crossing over, Morgan and his students find some crossover modifiers. Sturtevant attempts to find the loci of the CIIIB modifier via many careful experiments. An explanation of complex inheritance is not his end, as Waters says:

In order to map the region around the CIIIB modifier region, Sturtevant conducted many carefully orchestrated breeding experiments. These experiments produced inheritance patterns, which he subsequently explained. These explanations, however, were not what made Sturtevant’s work on CIIIB so important. Finding explanations for the complex inheritance patterns exhibited in his carefully arranged breeding experiments was the means rather than the ends. (Waters 2004: 791)

According to the discussion above, both of Darden’s and Waters’ approaches emphasize scientific practice, but focus on different aspects. The former one focuses on mechanisms but the later focuses on phenomena. Both of them reject reductionism and go beyond antireductionism in different directions. In their approaches, the methodological relationship between classical genetics and molecular biology has been eliminated, because biologists did not use the reductive methodology to advance the latter from the former. However, one should not see Darden and Waters as antireductionist, because they develop their methodologies centered on discovery and practice, rather than on explanations and theories on which antireductionists focus. For both,
explanation and theories are nothing but means or byproducts of discoveries. As a consequence, the old problem around the debate over reductionism and antireductionism shifts to a new problem of whether there is a common methodology for both classical genetics and molecular biology. Darden and Waters respectively provide a new framework. Both emphasize the key role of discovery in the advancement of the two disciplines, but suggest different directions and ends. Darden holds a direction towards discovering and integrating new mechanisms, while Waters does so towards investigating new phenomena. What are the two new methodologies?

4. The methodology of discovering mechanisms and the methodology of investigating phenomena

How did scientists who worked in classical genetics and in molecular biology discover new mechanisms? What methodology did they use to make new discoveries? From many biological sciences including classical genetics, cytology, molecular biology, neurobiology, and so on, Darden (1991, 2006) and Craver and Darden (2013) extract a methodology actually used by scientists in their discoveries. It is a mechanism-centered methodology, and its procedure can be described as follows.

In order to discover the mechanism underlying some phenomenon, Darden shows, scientists first conceive a mechanism sketch, which indicates a direction to which scientists should search. For example, molecular biologist James Watson supposed a sketch of flow of information for protein synthesis in 1954 (Fig. 1).

![Figure 1: Watson’s Sketch of Flow of Information](recreated by the author, based on Figure 1.4 in Darden 2006: 31)

According to this sketch, Watson suggests a mechanism schema to explain how protein is synthesized. This schema assumes that RNA has “Gamow holes” whose shapes are determined by the surrounding bases. “Different amino acids would then fit into different holes. … After amino acids fell into the holes, adjacent amino acids
would covalently bond (an electro-chemical activity) to one another, forming the protein.” (MDC 2000: 20) This schema is plausible, but soon disconfirmed by evidence. Mechanism schema that abstractly describes a specific type of mechanisms is a key notion in the mechanism-centered methodology. As Darden’s says:

Scientists do not always provide complete descriptions of mechanisms at all levels in a nested hierarchy. Also, they are typically interested in types of mechanisms, not all the details needed to describe a specific instance of a mechanism. We introduce the term “mechanism schema” for an abstract description of a type of mechanism. A *mechanism schema* is a truncated abstract description of a mechanism that can be filled with descriptions of known component parts and activities. (MDC 2000: 15)

A typical instance is Watson’s diagram of the central dogma of molecular biology.

![Figure 2: Watson's diagram of the central dogma (recreated by the authors.)](image)

If an abstract schema is filled with descriptions of known component parts and activities, then it can be instantiated as schemata in different degrees of abstraction.

Schemata exhibit varying degrees of abstraction, depending on how much detail is included. Abstraction may be constructed by talking an exemplary case or instance and removing detail ⋯ When instantiated, mechanism schemata yield mechanistic explanations of the phenomenon that the mechanism produces ⋯ Mechanism schemata can also be specified to yield predictions. (MDC 2000: 15–17)

A mechanism sketch is obviously a black box in which we do not know what entities and activities the target mechanism has. A mechanism schema and its instantiated schemata are a grey box in which we know the functions of the mechanism. Finally, scientists may offer a complete description of the mechanism. In the methodology Darden outlines, the discovery of mechanisms is a process from incomplete sketches (as black boxes), through schemas and schemata (as gray boxes), to complete descriptions of mechanisms (as glass boxes with full visible contents).

In addition to the construction of mechanism schemas and schemata, interventions conducted in laboratories play an important role. Darden points out that ex-
Experimental interventions provide guidance for how to discover important parts in the target mechanism. In order to explore details of the target mechanism, experimenters may intervene in some known entities or activities, alter their conditions, and observe what will happen in the termination of the experiment. Special effects or changes produced by such an intervention provide evidence for a hypothesized schema (MDC 2000: 17). When scientists possess sufficient clear and detailed knowledge of a working entity and attendant activities in the target mechanism, they are entitled to be said *discovering the mechanism*.

Having outlined Darden’s mechanism-centered methodology, we turn to Water’s phenomenon-centered methodology. According to Waters, classical geneticists have developed a “genetic approach” in their research. Its end is directed toward *discovery of new phenomena*. Three steps outline the genetic approach used in classical genetics: (1) To identify naturally occurring or artificially produced mutants; (2) to give genetic analyses of the mutants; and (3) to recombine the mutants to reveal a more basic biological process (Waters 2008: 255). This approach helps classical geneticists identify and locate many genes in the four chromosomes of fruit flies. It also dramatically increases the investigative utility of classical genetics. The genetic approach is not only a proper method for classical genetics, but also applied by molecular biologists for the investigation of new phenomena in molecular terms.

How do molecular biologists retool the genetic approach in their practice? First, they need to “re-conceptualize” classical genetics - that is, to reconstruct the basic theory or theoretical principles in classical genetics in terms of concepts in molecular biology. More precisely, they need to redefine “what is the gene” and re-explain the principle of genetic differences in the molecular language. Second, they have to “retool genetics,” applying the genetic approach used by classical geneticists to find out causal relations between a mutant’s phenotypes and genetic actions to molecular study via engineering DNA. Waters uses a recent neurological research to illustrate his account.

In 2007, M. Hammarlund, E. Jorgensen, and M. Bastiani wondered what the function of β-spectrin protein in neuron was. Previous investigators had already discovered that β-spectrin is located in the growth cones of nerve cells. This led to the hypothesis that β-spectrin plays a functional role in the early growth of those neurons. In order to test the hypothesis, they conducted a series of experiments, in which the first stage of them was:

They began by inserting a gene for green fluorescent protein (GFP) under the control of a regulatory region that distributed this protein in the growth cone of nerve cells. This enabled them to observe growth of nerve cells as they extended from the ventral side to the dorsal side during embryogenesis. Next, they used a mutation of *unc-70* to observe what happened to the
growth pattern of these cells in the absence of β-spectrin. They observed that the growth pattern was not disrupted. This result conflicted with the idea that the function of β-spectrin was to facilitate the outgrowth of axons and dendrites. (Waters 2008: 256–257)

After learning that most neurons developed normally, they tried to investigate neurons’ defects in mature neurons. “We found that neurons with defects—wandering, branched, or broken commissures—were rarely observed in wild-type animals at any time point. Defects were also rare in β-spectrin mutant embryos. However, β-spectrin mutant animals accumulated defects with time.” (Hammarlund, Jorgensen and Bastiani 2007: 270) They learned that the role of β-spectrin is not to facilitate their growth. To solve the puzzle, they made another conjecture that there would be two possible functions of β-spectrin and conducted a series of ensuing experiments with various manipulative methods.

First, β-spectrin might be involved in the addition of membrane to axons during growth of the organism (Morris 2001). Because worms increase in length and circumference during development, failure to insert membrane into axons could cause them to break. Alternatively, β-spectrin might protect neurons against the acute strains caused by movement. (Hammarlund, Jorgensen and Bastiani 2007: 272)

To figure out these two possibilities, the neuroscientists paralyzed the mutant worms by using RNAi to intervene the expression of muscle myosin gene (unc-54). They found that the rate of the defective neurons of non-paralyzed worms lacking β-spectrin is higher than the rate of paralyzed worms (4.8%:1.3%). This indicated that non-paralyzed neurons that lack β-spectrin are more sensitive to acute strains caused by movement than those immobilized worms (the place of explanatory reasoning). The results were checked by intervening the expression of another gene (unc-22 (e66) allele/Twitchin), which also prevented worms from moving in another way (the place of investigative reasoning). This led the neuroscientists to conclude that the role of β-spectrin is to protect neurons against breakage caused by movement-induced acute strain rather than during the process of neuronal membrane addition during growth. (Hammarlund, Jorgensen and Bastiani 2007: 272)

In Waters’ view, the neuroscientists applied the genetic approach that consists of (1) artificially producing mutants (“[they] used a mutation of unc-70 and others to observe what happened to the growth pattern of these cells in the absence of β-spectrin”), (2) giving genetic analyses (“[they] found that the rate of the defective neurons of non-paralyzed worms ··· higher than the rate of paralyzed worms”), and (3) recombining the mutant to reveal more basic biological process (“The result were checked by intervening the expression of another gene ···”). After several steps, they
finally discovered the function of $\beta$-spectrin. All stages of the procedure show that molecular biologists have never abandoned the genetic approach and investigative methods that classical genetics have used to produce great utilities. In these experiments the neuroscientists manipulated some DNA expressions at gene level, but did not build up the research achievement in terms of genes and DNA. Genes are used as tools to investigate new phenomena. “This example illustrates ··· an investigative strategy, without being guided by a comprehensive gene-centered theory about the phenomena to be explained.” (Waters 2014: 136) Strengthening the investigative utilities is just the goal of geneticists, whether classical or molecular. As a consequence, that classical genetics was retooled by molecular biologists to investigate novel phenomena in terms of the molecular language is truly an adequate methodology for the two biological fields.

5. The dialectics between ends and means: Integrating the methodologies

We agree with Darden’s approach, because this approach grasps the fundamental and essential methodological features of biological practices, i.e., discovery of mechanisms. The discovery of a variety of mechanisms leads to biological research, including the discovery of new phenomena and construction of theories. The history of classical genetics and molecular biology shows that the knowledge of mechanisms in different levels provides a blueprint for scientists to intervene and manipulate working entities (organisms, genes, DNA, RNA, proteins, etc.) to investigate what effects or phenomena would happen. By means of such operations, many new phenomena have been discovered and theories of genetics constructed (Darden 1991). In this sense, the discovery of new phenomena and construction of theories depend on the discovery of mechanisms. However, in some cases, the discovery of mechanisms in turn depends on the discovery of phenomena, because new phenomena offer motives to discover underlying mechanisms. The case in which Mendel, the perceived founder of classical genetics, discovered certain ratios of contrast traits offers a standard example. In this respect, Waters’ emphasis on the methodology for investigation and discovery of new phenomena supports the mechanism-centered approach. Hence, we think that the two approaches are complementary and respectively grasp adistinctive aspect of the whole methodology. We believe that the two are able to be integrated so as to provide a more complete account for biological practices. We argue that this account is an experiment-based methodology that can satisfactorily serve both classical genetics and molecular biology.

According to Waters’ approach, the investigation of new phenomena is an essential feature of both classical genetics and molecular biology. Waters argues that molecular biologists retool classical genetics as investigative levers, but he does not show how biologists appropriately treat new phenomenon in a way that is indepen-
dent of the theory-driven approach. There is a blank between genetic analyses and more basic biological processes in his methodology. We think that the organization of experimental data is the key. From their experiments, what scientists have gotten is only unorganized experimental data. If they cannot organize those data into a “significant” phenomenon, then they would not discover anything new.

Chen’s article on Mendel’s experimental discovery emphasizes the status of experimental data in the development of classical genetics (Chen 2013). In that article, Chen takes Mendel’s discovery as an example, arguing that there are experimental discoveries that are independent of theories. Differing from the typical story told by biology textbooks, Chen argues that Mendel made an experimental discovery via establishing two data models to represent two distinctive ratios of contrast traits. Mendel’s discovery of new phenomena was independent of any preceding theory of heredity, because Mendel did not have a theory of heredity. He performed a series of breeding experiments on peas based on his background ideas of hybridization and development. Other classical geneticists have used his experimental discovery as a tool to investigate genetic phenomena.

According to Chen’s argument, experimental discovery usually precedes the discovery of mechanisms and works as a prerequisite for the latter. It plays a role in three ways: organizing data into significant phenomena (that is, discovering new phenomena); producing the need and motivation to discover mechanisms; and constraining the direction for construction of theoretical hypotheses (Chen 2013: 115–117). As we have seen, the concept of mechanism also plays an important role in Chen’s analysis. Thus, his account seems to be able to work as a basis to integrate Darden’s and Waters’ approaches.

The key point in Chen’s argument, we think, is that scientists organize experimental data into significant phenomena via building (experimental) data models. As they establish correct data models, they make the discovery of phenomena. “The discoverer does so by constructing adequate and correct models to organize fragmentary data, endow data with significance, and reveal hidden structures, patterns, and regularities.” (Chen 2013: 117) Data models usually are represented by diagrams or figures. In his article, Chen interprets that Mendel’s two laws of heredity are nothing but only two data models that can be represented by two diagrams, which represent two ratios of traits (A: a = 3:1 and AB: Ab: aB: ab = 9:3:3:1) (Chen 2013: 112). The two data models represent the significant phenomena produced from “the combination and transmission of traits in some certain crosses between true-breeding forms and hybrids.” (Chen 2013: 113)

We think that Chen’s methodological framework of experimental discovery can be extended to molecular biology— for example, the case examined by Waters. Applying the notions of data models to Waters’ case, we note that the neuroscientists depicted three important figures based on the observation and classification of the
experimental outcomes. In Chen’s analysis of Mendel’s case, he suggests a hierarchical framework of models, theories, experiments, data, and phenomena (Chen 2013: 113; See Fig. 4 below). As he says: “··· a model of experimental procedure can guide the performance of an experiment and produce raw data. It can also provide a frame for a data model to organize raw data produced from the experiment.” (Chen 2013: 113) In other words, an experimental procedure provides a framework to organize raw data into a data model.

According to Hammarlund, Jorgensen, and Bastiani’s description of experiments, we reconstruct models of experiments or experimental procedures designed by these neuroscientists. The common end of those experiments is to compare the expression of some traits (in growth) of neurons in the wild type of and in the intervened type (unc-70) of worms. Some traits are seen as normal, while others are defective. Therefore, they got experimental outcomes from the two different genotypes of neurons in worms. In order to understand the meaning of experimental outcomes, the scientists have to depict the outcomes into figures to compare them. Those figures with experimental data present various proportions from experimental outcomes, and different proportions represent the occurrence frequency of particular phenotypes under the certain experimental conditions. They should be adequately regarded as data models. The data models exhibit some specific pattern, regularity, or biological meaning hidden under the new phenomenon that neuroscientists discovered.

Figure 3.1 illustrates that neurons lacking β-spectrin still develop normally in rough from the percentage of growth cones with specific morphologies. The scientists say, “Finally, we found that a similar fraction of neurons had successfully completed their migration (formed T shapes on the dorsal cord) in wild-type and mutant embryos.
(fraction of neurons forming T shapes: wild type = 61%; unc-70 (s1502) = 61%).” (Hammarlund, Jorgensen, and Bastiani 2007: 270) They learned that β-spectrin is not essential for normal axon outgrowth of the neurons in the first experimental stage, which suggested to them to investigate the accumulation of specific defects at three time points: the point of embryogenesis, of just-after-hatching, and of at-24h-after-hatching. Figure 3.2A shows that neurons in wild type and in unc-70 type accumulate defects with time; Fig 3.2B offers a disparate percentage of neurons with specific defects in wild type and in unc-70 type. These outcomes demonstrate that β-spectrin prevents the accumulation of defects in the developmental processes of neurons.

In the third stage of this experiment, the scientists paralyzed worms by manipulating the expression of the gene for myosin, using RNAi to interfere with unc-54 that encodes a muscle myosin. Their findings present that the neurons of paralyzed worms lacking β-spectrin (RNAi of unc-54/myosin) largely maintained the structure. Figure 3.3 shows that the interfered muscle myosin (RNAi of unc-54) rescues neuronal defects in unc-70 worms. Non-paralyzed and lacking β-spectrin neurons had a mean of 4.8 defects per animal. In contrast, paralyzed and lacking β-spectrin neurons had a mean of 1.3 defects. RNAi of unc-54/myosin had no effect on wild-type worms.

Checking β-spectrin indeed could prevent neurons from the strains caused by movements. As such, the scientists manipulated another gene, unc-22, which encodes the muscle protein Twitchin. The mutant worms are also incapable of moving in another way. They found that the interfered worms lacking β-spectrin largely maintain the same structure as that of the worms with β-spectrin. “We found that the genetic loss of Twitchin in the β-spectrin mutant background resulted in paralyzed animals with fewer neuronal defects than β-spectrin mutants alone.” (Hammarlund, Jorgensen, and Bastiani 2007: 272) All of these outcomes indicate that lacking β-spectrin has no effect on the normal development of neurons and that the function of β-spectrin is to protect neurons against breakages caused by movements.

Why can these figures be regarded as data models? What offers structures for them and makes them be models? The figures represent organized experimental outcomes. Models of experiments with experimental procedures designed by scientists offer structures to organize those outcomes (data) into models. Figures 3.1, 3.2, and 3.3 indicate that all models of experiment are designed based on a comparison between the trait expression of the wild type and that of the intervened type (unc-70). The next question is: Why can β-spectrin protect neurons against strains? They cannot answer this question, because “... the mechanism for the elasticity of axons and dendrites is unknown, as is the response of neurons to breaks caused by the loss of elasticity.” (Hammarlund, Jorgensen and Bastiani 2007: 269) If the scientists wish to answer this question, they have to discover a mechanistic explanation! However, since the scientists have learned the function of one component (β-spectrin) and the activity (protecting) in which the entity participates, they will be able to find a sim-
ple mechanism underlying the phenomenon (the strains caused by movements). In addition, they learn that the entity ($\beta$-spectrin) plays no role in the mechanism underlying the development of neurons, although they have not yet described the whole developmental mechanism.

This case of molecular biology illustrates that experimental discovery of new phenomena provides key contributions to the discovery of the molecular mechanisms of specific traits and functions. It not only fills in the gap in the genetic approach, but also knits Darden’s mechanism-centered and Waters’ phenomenon-centered methodologies.

A final question arises. We note that the mechanism-centered approach regards the discovery of mechanisms, while the phenomenon-centered approach regards the discovery of new phenomena, as the end of both classical genetics and molecular biology. Which one, the discovery of new mechanisms or the investigation of new phenomena, is the end of biological practices? We think that there are different ends and means in different stages of scientific research. In some stages, explanations or mechanism schemas are used as the means to achieve the end of discovering new phenomena; in some other stages, the investigation of new phenomena is used as a starting point to discover a new mechanism or to puzzle out the whole of a known but incomplete mechanism or to construct an integrative theory. For example, the classical geneticists Morgan and his students such as Sturtevant, Bridge, and Beadle indeed discovered many new phenomena of heredity, but they also endeavored to discover new mechanisms and constructed a comprehensive theory.\(^4\) The evidence is shown by Morgan and Sturtevant’s *The Mechanism of Mendelian Heredity* (1915) and Morgan’s *The Theory of the Gene* (1926). Similarly, Hammarlund, Jorgensen, and Bastian indeed succeeded in promoting the investigative utility of their approach, but they also think that their research helps search for an underlying mechanism. It is difficult for us to say which is the end or which is the mean in classical genetics and molecular biology.

Why do we not see an investigation of new phenomena, a discovery of new mechanisms, and a construction of new theories from a dialectic point of view? Indeed, the three types of conducts occur in different stages of scientific research in a circular way, constituting an overall process of scientific practices for both classical genetics and molecular biology. Chen (2013: 113) suggests a hierarchical framework of models to show the interrelations among theories or theoretical principles, models of mechanisms, phenomena, raw data, data models, and models of experiments, see Fig. 4.

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\(^4\) Here, the term “theory” is used in a grand sense - that is, mechanism schemas, mechanism schemata, and mechanism scaffolds are theoretical. Conversely, one may say that a theory in classical genetics or molecular biology contains many mechanism schemas, schemata, and scaffolds.
Theoretical principles (or principled models)
↓ de-idealized

Models of mechanisms
↓ explaining

Phenomena
↓ ↑ providing frameworks for data models

Data models ←——— Models of experiments (experimental procedures)
↑ organized ↓ guiding

Raw data (out of the world) ←—— experiments

Figure 4 A hierarchical framework of theories, mechanisms, and experiments

According to Chen, “[t]he framework shows that a model of experimental procedure can guide the performance of an experiment and produce raw data. It can also provide a frame for a data model to organize raw data produced from the experiment. Representational models can be obtained by de-idealizing principled models and be used to explain phenomena revealed by data models.” (Chen 2013: 113–114) Here we would like to extend Chen’s hierarchical framework of models to a dialectic or circular structure, as Fig. 5 shows. We believe that the extended framework reflects a more
complete process of scientific practices in classical genetics and molecular biology, on the one hand; and can integrate Darden’s and Water’s methodology, on the other hand.

This framework reflects a dialectical view on the discovery of phenomena (the construction of data model), the discovery of mechanisms (the construction of models of mechanisms), and the construction of theories (theoretical principles). On the one hand, one sees that the discovery of phenomena depends on the construction of data models, and the latter in turn depends on experimental procedures; on the other hand, the discovery of mechanisms is motivated by the discovery of significant phenomena, and the former can also lead to designing models of experiments. All of these show that an experiment is just the basis of a methodology that works in classical genetics and molecular biology.

6. Conclusion

Both theoretical reductionism and theory-centered antireductionism have failed to provide an adequate account of the methodological relationship between classical genetics and molecular biology. Darden and Waters independently suggest new and different approaches via a refocus on scientific practice. However, their methodologies are partial to their respective preferences. We suggest integrating the two methodologies in order to provide a more complete picture. As a result, we propose an experiment-based methodology that is at work in classical genetics and molecular biology. This methodology also regards the investigation of new phenomena, the discovery of new mechanisms, and the construction of new theories as both means and ends in a circular way in the developmental process from classical genetics to molecular biology.

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