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8 Mechanisms and Models

> Generally speaking, making models for unknown mechanisms is the creative process in science.
>
> Harré 1970, 40

1. INTRODUCTION: MECHANISMS AND MODELS

Biologists often seek to discover *mechanisms*. Knowledge of biological mechanisms is valuable because descriptions of them often play the roles attributed to general scientific theories. They provide explanations of puzzling phenomena. They enable biologists to make predictions. They aid the design of experiments. They may explain domains of wide scope. They may make possible medical or biotechnological interventions for practical purposes. Especially in molecular biology, theories consist of sets of mechanism schemas, such as those for DNA replication and protein synthesis.

Biologists use many types of *models* to represent and discover mechanisms: diagrammatic models, physical scale models, analogue models, model organisms, in vitro experimental systems, mathematical models, computer graphic and simulation models. Models represent and substitute for the thing modeled, while being easier to understand, manipulate, or study. Choice of an appropriate model depends on the problem to be solved using it. In medicine, animal models are often used when the goal is to understand disease mechanisms in humans. Molecular biologists use bacteria and viruses as models for mechanisms with domains of very wide scope, such as DNA replication.

The topics here are mechanisms in biology and models that aid their discovery. Section 2 provides a characterization of mechanisms, based

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on cases from molecular and neurobiology. Section 3 introduces the distinctions among mechanism schemas, their instantiations, and incomplete sketches; the term "model" in the sense of a theoretical model may refer to any of the three. Several kinds of models aid the discovery of mechanisms, especially analogue models, model organisms, and in vitro experimental systems; they are the subject of Section 4. Section 5 examines the use of such models in reasoning to discover mechanisms, which is an extended process of generating, testing, and revising mechanism sketches and schemas. Finally, the conclusion points to general philosophical issues and to unanswered questions in this new research program on mechanisms in biology.

2. CHARACTERIZATION OF BIOLOGICAL MECHANISMS

A mechanism is sought to explain how a *phenomenon* is produced. Mechanisms may be characterized as entities and activities organized such that they are productive of regular changes from start or setup to finish or termination conditions (Machamer, Craver, and Darden 2000, 3). The nature of the *phenomenon* for which a mechanism is sought provides important guidance in discovery. Biologists seek the location of the mechanism and find places for its beginning, ending, topping off, bottoming out, and boundaries, guided in part by the nature of the phenomenon. Many biological mechanisms are *regular* in that they usually work in the same way under the same conditions. The regularity is exhibited in the typical way that the mechanism runs from start to finish, thereby producing and reproducing a given phenomenon. For example, the phenomenon of DNA replication is produced by the mechanism of DNA replication. The mechanism begins with one double helix and ends with two. One double helix unwinds and each half provides a template along which complementary bases are aligned, yielding two identical helices at the end. The description of this mechanism bottoms out at the level of parts of the DNA molecule, including the bases and their charges. The precise hydrogen bonding between bases (usually) produces accurate copying of the order of the bases from the parent strands to the daughter ones. The topping-off point for the description of this mechanism is the entire double helix, a macromolecule within the nuclei of cells.

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Mechanisms are composed of both *entities* (with their properties) and *activities*. Activities are the producers of change. Entities are the things that engage in activities. For example, two entities, a DNA base and its complement, engage in the activity of forming hydrogen bonds because of their properties of geometric shape and their arrangements of weak polar charges. Entities and activities are interdependent. For example, polar charges are necessary for hydrogen bond formation. Appropriate shapes are necessary for lock and key docking of enzymes and substrates. This interdependence of entities and activities allows biologists to reason about entities on the basis of what is known or conjectured about the activities, and vice versa. Such reasoning by forward or backward chaining aids discovery of subsequent or prior stages, based on what is known or conjectured about adjacent ones.

For the purposes of a given biologist, research group, or field, there are typically entities and activities that are accepted as relatively fundamental. In other words, descriptions of mechanisms in that field typically *bottom out* and *top off* in particular places. Those places may be more or less arbitrarily chosen. For example, memory mechanisms are investigated at many mechanism levels, from a mouse learning a maze to two neurons (cells) exchanging neurotransmitters (molecules). Alternatively, appropriate bottoming out and topping off may be dictated by the nature of the phenomenon and the kinds of working entities that are active in mechanisms. In molecular biology, mechanisms typically bottom out in descriptions of the activities of molecules (macromolecules, smaller molecules, and ions) and cell organelles (e.g., ribosomes). These entities are the *working entities* of molecular biological mechanisms, such as DNA replication and protein synthesis. Smaller (or larger) entities do not have the requisite sizes, shapes, charges, or other activity-enabling properties to play roles in these molecular mechanisms.

Mechanisms have *productive continuity* between stages: that is, the entities and activities of each stage give rise to the next stage. There are no gaps from the setup to the termination conditions. Mechanisms have a *beginning* and an *end*, again more or less arbitrarily chosen. For instance, a natural beginning point for the mechanism of DNA replication is one double helix, and a natural ending is two double helices. However, in an ongoing series of mechanisms, some of which might be cyclic, the choice of

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start and stop points may be based merely on the convenience of investigation.

Mechanisms should be distinguished from machines. A machine is a contrivance, with organized parts designed to work together smoothly. Mechanisms are often associated with machines because mechanisms are most conspicuous in human artifacts, such as the mechanical clock. A stopped clock is still a machine, but it is not a mechanism. Mechanisms are active. Human artifacts may exhibit the optimal results of engineers' effective and efficient designs. However, living things are a result of evolutionary tinkering and satisficing. As Michael Ruse noted, the idea that the world is full of designed machines has been replaced by the idea that it contains evolved machines, built in a ramshackle way as evolution fashions their adaptations from available parts. Although organisms may be viewed as ramshackle machines, an organism, as a whole, is not a mechanism. Many mechanisms operate within a living organism. Moreover, looking up instead of down, organisms may be said to play roles in higher-level mechanisms, such as the isolating mechanisms leading to speciation.

3. DESCRIPTIONS OF MECHANISMS: SCHEMAS, SKETCHES, AND THEORETICAL MODELS

Biological theories represented by sets of mechanism schemas may be contrasted with philosophers' analyses of theories as sets of syntactic formal axioms or as abstract and idealized formal semantic structures. (The sense of formal "model" in this semantic conception of theories will not occupy us here.) Analysis of mechanistic theories in biology does not import a formal structure to understand theories, but instead strives to characterize mechanisms and their representations in a manner faithful to biologists' own usages. Scientists use theories to describe, explain, explore, organize, predict, and control the items in a theory's domain. Descriptions of mechanisms aid all of these tasks (Craver 2002a).

Adequate descriptions of mechanisms include a description of the phenomenon produced by the mechanism, the entities and activities composing the mechanism, their setup conditions, along with their productively continuous spatial and temporal organization. Spatial organization includes localization, structure, orientation,

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connectivity, and compartmentalization (if any). Temporal organization includes the order in which activities occur; their rate, duration, and frequency; and the overall order of the stages of the mechanism (Darden 2006, chap. 12).

A *mechanism schema* is a truncated abstract description of a mechanism that can be filled with more specific descriptions of component entities and activities. An example is this diagram of the central dogma of molecular biology:

DNA → RNA → protein

This is a schematic representation (with a high degree of abstraction) of the mechanism of protein synthesis. A less schematic description of a mechanism shows how the mechanism operates to produce the phenomenon in a productively continuous way and satisfies the componency, spatial, temporal, and contextual constraints. The goal in mechanism discovery is to find a description of a mechanism that produces the phenomenon, and for which there is empirical evidence for its features. A mechanism schema can be instantiated to yield such an adequate description.

In contrast, a *mechanism sketch* cannot (yet) be instantiated. Components are (as yet) unknown. Sketches may have black boxes for missing components whose function is not yet known. They may also have gray boxes, whose functional role is known or conjectured; however, what specific entities and activities carry out that function in the mechanism are (as yet) unknown. The goal in mechanism discovery is to transform *black boxes* (components and their functions unknown) to *gray boxes* (component functions specified) to glass boxes (components supported by good evidence). A schema consists of *glass boxes* – one can look inside and see all the parts. Incomplete sketches indicate where fruitful work may be directed to produce new discoveries. The transition from sketch to schema may be a continuous process, as various portions of the mechanism are discovered in a piecemeal way. An instantiated schema shows details of how the mechanism operates in a specific instance to produce the phenomenon. Hence, mechanistic theories explain the phenomena in their domains.

As William Bechtel and Adele Abrahamsen (2005) noted, explaining a phenomenon involves describing the mechanism responsible for it, often by constructing a model that specifies key

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parts, operations, and organization and that can simulate how their orchestrated functions transform certain parts. The term "model" here refers to a model of a mechanism or what philosophers might call a "mechanistic theoretical model." "Model" in this sense may refer to any of the three terms discussed: a mechanism "schema," an "instantiation" of a mechanism schema, or a "sketch." Sometimes the terms "theory" and "model" in this sense of theoretical mechanistic model are used synonymously, in which case a mechanism schema or a set of mechanism schemas is appropriate. Sometimes a model is said to be an instance of a theory, showing how an abstract theory is to be applied in a particular case, in which case an instantiation of a mechanism schema is appropriate. Sometimes a proposal is called a "model" because components are as yet unspecified, in which case it designates an incomplete mechanism sketch.

The scope of the domain modeled varies. A mechanism schema may represent a single unique case (e.g., a mechanism producing a unique historical event) or a recurring mechanism in only one species (e.g., a disease-producing mechanism in one form of human cancer). More often, mechanism schemas have a "middle range" (Schaffner 1993) of applicability; that is, they are found in some subset of biological cases, such as memory mechanisms in the hippocampus of vertebrates. In a few cases, a schema may be claimed to apply to all known cases, such as all instances of protein synthesis in living things on Earth.

Again, consider the diagram for the mechanism of protein synthesis:

DNA → RNA → protein

This is a simplified and general schema of the protein synthesis mechanism. It is very schematic and abstract; at this degree of abstraction it may be instantiated in a domain of very wide scope. It applies to most instances of protein synthesis in living organisms found on Earth. But compare the following schema:

RNA → DNA → RNA → protein

This diagram is at the same degree of abstraction as the previous one, but it has a domain of much narrower scope, namely, retroviruses. Hence, the degree of abstraction with which the mechanism schema is represented and the scope (that is, the generality) of the domain

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modeled are distinct. Increasing the degree of abstraction may produce a schema with a higher degree of generality, but not necessarily so, as these examples illustrate.

The amount of detail specified in an abstract mechanism schema is called the ''degree'' of abstraction. Abstraction hierarchies have an increasing loss of detail as one ascends the hierarchy. Conversely, as one descends the hierarchy, there is increasing ''specification'' of detail until the schema is ''instantiated,'' resulting in the description of a particular mechanism. Thus, a mechanism schema should not be viewed as a model with merely the two-place relation of a variable and its value; mechanism schema hierarchies may have a range of degrees of abstraction. The term ''degree'' is used to refer to rungs in abstraction hierarchies while the term ''level'' refers to rungs in part-whole hierarchies among nested mechanisms (usually represented at roughly the same degree of abstraction).

In biology and philosophy of biology, the term ''model'' is used in many ways, such as to refer to mechanism schemas, their instantiations, sketches, and hierarchical mechanistic theories. A different but also common usage is employed to refer to something relevantly similar to the mechanism of interest and used in its representation or discovery. To models of this latter type we now turn.

4. MODELS FOR DISCOVERING MECHANISMS

Many kinds of models aid the discovery of mechanisms. Models have both a ''subject'' and a ''source.'' The mechanism to be discovered is the ''subject'' of the model. The ''source'' of the model may be the subject itself, as in the case of physical scale models and computer simulation models. In contrast, the source of a model may be different from the subject mechanism of interest, as in the case of an analogue model or a model organism used as a substitute for studying mechanisms in humans (Harré 1970).

Diagrams are a type of model used to represent the mechanism of interest; they have the same source and subject. Diagrams are especially propitious for representing many mechanisms. They show overall spatial organization of the parts and depict more or less structural detail of the entities. Activities are more difficult to represent in static drawings. Sometimes arrows illustrate activities, but arrows are also often used to show mere movement or time

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slices. Cognitive psychologists have studied how humans manipulate visual representations in order to run "mental simulations" of mechanisms. This method enables the person to "see" how some mechanisms work and to use the representation to make predictions (discussed in Bechtel and Abrahamsen 2005). But in more complex cases, humans use aids, such as computer simulations, to represent the complex mechanism and to run a simulation to make a prediction and explore "what-if" scenarios. Jim Griesemer (2004, 438–39) intriguingly noted: "Although interactive graphics extended the tradition of physical modeling, they also constituted a new mode of interaction with numerical data, allowing users to intervene kinesthetically in the simulation process. This is terra incognito for conventional philosophies of scientific knowledge."

A physical scale model of DNA has the same source and subject. In a famous case, the x-ray crystallographer Rosalind Franklin produced x-ray photographs by bombarding crystallized DNA (both the source and the subject). James Watson and Francis Crick used her photographs in choosing the shape and dimensions of their physical scale model of the DNA double helix. Although the x-ray crystallographic data (as well as other data about the chemical composition of DNA) constrained the space of possible models, those constraints were insufficient to determine all the physical properties of DNA (the source and subject) to use in building the scale model. In *The Double Helix*, Watson recounts the moment when he physically manipulated accurately constructed physical models of the DNA bases. That tactile manipulation in two dimensions (based on the assumption that the bases were flat and in a plane) allowed him to discover the geometric fit and hydrogen bonding between complementary bases. This discovery illustrates the role that may be played by physical manipulations of scale models. It was one step among many in this two-year extended discovery episode. The double helix model with its two strands of complementarily bonded bases suggested to its discoverers how it could carry out one of the functions of the genetic material. They immediately proposed the mechanism of DNA replication via the activity of complementary copying to fill the black box of genetic replication in the series of hereditary mechanisms. Thus, the *model of* DNA served as a *model for* investigating the functions of the genetic material. (For more on this distinction of *model of* and *model for*, see Griesemer 2004.)

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Two-dimensional diagrams, three-dimensional physical scale models, and computer graphic models may all be generated by using data about the subject being modeled. To see how the structures can possibly function, researchers locate the activity-enabling properties of the entities. Examples include the hydrogen bonds between bases or the active sites of enzymes. Those activity-enabling properties suggest to humans or to computational discovery programs what the activities and stages of the mechanism may be. Drug discovery programs readily exploit such knowledge of active sites on molecules to design new chemicals to play desired roles in disease prevention mechanisms.

Standing in contrast to such models, in which the source and subject are the same, are analogue models, in which the source for the model differs from the subject itself. Distant and near analogies, model organisms, and model experimental systems are examples. An analogue model is more or less similar to the subject of interest. In her classic *Models and Analogies in Science*, Mary Hesse (1966) coined useful terms for the similarities and differences between the analogue and the subject. The components that they both share are the ''positive analogy.'' The components that are dissimilar are the ''negative analogy.'' The components whose relation has yet to be determined at a given stage in the use of the analogy are the ''neutral analogy.'' Scientists have often used analogies in discovering new scientific theories. Examples abound in Keith Holyoak and Paul Thagard's (1995) *Mental Leaps: Analogy in Creative Thought*. The discovery of mechanisms is no exception.

Those working on the use of analogical reasoning to construct scientific hypotheses break it down into stages: problem finding, analogue retrieval, extraction of an abstract causal structure from the analogue, mapping from analogue structure to the subject area, adjustments to fit the subject, and testing of the newly constructed hypothesis. First, one identifies the problem to be solved. For example, one wishes to understand the mechanism of regulation of the genes producing the enzymes for synthesizing the amino acid tryptophan (trp). Then one searches to retrieve an appropriate analogue. For example, one might be familiar with the model for regulating the set of genes for producing the enzymes for digesting the sugar lactose; the lac operon model works via a derepression mechanism. The next stage is extracting an abstract mechanism

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schema from the detailed analogue. For the lac operon model, one might drop the details specific to the lactose case to construct an abstract derepression mechanism schema. In such an abstract schema, a gene produces a repressor protein molecule that binds to an operator gene on the DNA just upstream for a set of coordinately controlled structural genes. When an external inducer is present (the milk sugar lactose), it serves to bind to the repressor and change its shape; as a result the repressor falls off the DNA. Once the repressor falls off the DNA, the adjacent structural genes become active. This abstract derepression schema may be mapped to the subject area for the tryptophan case. Adjustments must be made because of the differences in the trp case. The trp genes are expressed when certain concentrations of tryptophan are not present. So tryptophan, when bound to the repressor, allows it to bind to the DNA and repress the genes. In the absence of suitable concentrations of tryptophan, the repressor does not bind to the DNA. Thus, one can generate a mechanistic model for the regulation of the tryptophan genes by analogy with the lac operon and appropriate modifications.

Once one has generated a mechanistic hypothesis by analogy, it must be evaluated to see how well it fits the subject area. One uses it to predict the outcome of experiments on the trp system. However, anomalies arose during testing of the trp system. In fact, the trp operon was found to be more complex than the lac operon. The depression mechanism was acting, but something more was also happening. Resolution of the anomalies required the addition of another regulatory mechanism, called ''attenuation.'' This secondary mechanism operated to fine tune the concentration of the enzymes producing tryptophan, depending on the concentration of tryptophan in the bacterial cell. Sometimes when anomalies arise, the unexploited neutral analogy in the original analogue model may be a resource for ideas about how to revise the mechanistic hypothesis. However, in the trp case, new components not found at all in the lac case had to be added to resolve several anomalies (Karp 1989).

After the success of the operon model, it was used as an analogue to construct plausible hypotheses about how other genes were regulated. Some operate by a derepression mechanism, but others do not. The repertoire of types of gene regulation mechanisms continues to grow (Beckwith 1987).

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In addition to conceptual analogue models, biologists use physical analogue models, namely, model organisms and in vitro experimental systems. Such model systems may be used, in some cases, to map directly to the subject of interest; in other cases, they may be used in the discovery of a general theory. When the goal is to discover mechanisms in humans, often disease mechanisms, then animal models are sought or constructed and mappings are direct from the animal model to humans. However, in veterinary animal medicine, humans may be the model organisms for mechanisms involving possible pain produced by drugs or procedures. Humans can report their pain sensations, while inferences on the basis of physiological or behavioral cues in animals are much less reliable for judging the presence and severity of pain. Many such considerations guide the choice of model organisms, including the nature of the mechanism sought in the subject of interest, the belief that such a mechanism or a relevantly similar one operates in the model, the ease of manipulation, and the amount of work that has already been done on the model organism that can serve as a basis for further work (Burian 1993).

Schaffner extensively examined the use of model organisms in molecular biology and, more recently, in behavioral genetics (Schaffner 1993, 1998, 2001). As a result, he viewed some biological theories as having the structure of ''overlapping temporal models.'' These are theories of the ''middle range'': that is, their scope is not universal but, with variations, applicable beyond a single instance to a domain of middle-range scope, such as prokaryotes or vertebrates. Components of such theories are presented as ''collections of entities undergoing a process.'' In the mechanistic perspective proposed here, Schaffner was referring to theories composed of mechanism schemas with varying scope. A model organism or a model experimental system provides the ''prototype''; then, how widely the prototypical mechanism (or slight variants of it or its modules) occurs has to be determined empirically.

In biological, as opposed to applied, research, as Schaffner noted, the goal is often to find generalizations. A manipulable model is sought that will provide results that can be generalized. The model organism is the source for the general mechanism schema (the subject), as well as an instance of it. The history of biology is replete with examples not only of excellent model organisms, namely, those

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with typical mechanisms that were successfully generalized, but also of failed ones, namely, those with odd quirks that led their users astray in the search for general theories. Gregor Mendel's peas (*Pisum sativum*) have what others later discovered to be general hereditary mechanisms, while Mendel's attempts to extend his results to hawkweed (*Hieracium*) failed. Hawkweed, it was later found, can reproduce asexually, and thus was a very poor choice as a model organism for genetic crosses. Hugo de Vries studied the sudden appearance of new true breeding forms of evening primrose (*Oenothera*). He believed that the evening primrose was an excellent model organism for establishing a research program of experimental evolution in his botanical garden. However, the extremely rare chromosomal mechanisms in the evening primrose are not general at all. Considerable empirical work ensued to unravel the quirky mechanisms of hawkweed and evening primrose, more than would likely have been done had they not played the role of anomalous model organisms in the search for general hereditary mechanisms.

In contrast are the triumphal tales. T. H. Morgan's choice of the fruit fly (now named *Drosophila melanogaster*) for his genetic studies yielded understanding of very general hereditary mechanisms. Similarly, Jacques Monod's choice of the bacteria *Escherichia coli* led to the discovery of regulatory genes, a universally found component of gene regulation mechanisms, even though all are not the depression type (Darden and Tabery 2005). However, many anomalies arose for Monod's famous quip: ''What's true for *E. coli* is true for the elephant, only more so.'' Other molecular biologists, desiring to study mechanisms of cellular differentiation not found in bacteria, Sydney Brenner, for example, carefully chose and perfected strains of the nematode worm, *Caenorhabditis elegans* (discussed in Ankeny 2000), and François Jacob (1998) chose the mouse, *Mus musculus*.

Even when it fails, it is a good strategy to generalize from a mechanism discovered in one experimental system to others producing similar phenomena. Evolution often does reuse mechanisms or their components. As Francis Collins, then head of the U.S. Human Genome Project, said:

> Because all organisms are related through a common evolutionary tree, the study of one organism can provide valuable information about others. Much of the power of molecular genetics arises form the ability to isolate and

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understand genes from one species based on knowledge about related genes in another species. Comparisons between genomes that are distantly related provide insight into the universality of biologic mechanisms and identify experimental models for studying complex processes. (Collins et al. 1998, 686–87)

Because of the common evolutionary descent of biological organisms, biology has a stronger basis for appealing to similarity than other fields employing cross-field analogies. Many similarities are a result of evolutionary homology; that is, the similarities result from the subject and source's sharing a common ancestor. Thus, model organisms and model experimental systems may serve as homologues for studying the mechanism of interest. But evolution works both by copying and by editing, that is, both by inheritance and by variation. So, it is an empirical journey to find the appropriate family resemblances, in the literal sense of that term (Schaffner 2001).

As Marcel Weber (2005) pointed out, phylogenetic inferences based on homology provide a sounder basis for generalization than mere induction by simple enumeration. When a mechanism is found in organisms distant on the evolutionary tree, the assumption is made that all the descendants of their common ancestor share the same mechanism. This is, he noted, an argument from parsimony, but one that is plausible because of the unlikelihood that the same mechanism did arise independently in widely separated evolutionary paths. His examples of widely shared homologous mechanisms included the mechanisms of DNA replication and protein synthesis in all eukaryotes.

Even more often than the evolutionary conservation of entire mechanisms, modules of mechanisms are reused in other mechanisms. Model organisms have supplied what Weber called materials for "preparative experimentation." For example, DNA sequences extracted from *Drosophila* were used as probes to fish for homologous DNA sequences in genomic libraries prepared from the DNA of a variety of other organisms. The important homeobox genes discovered in *Drosophila* are an example. Homeobox genes control the development of the front and back parts of the body. DNA sequences almost identical to those from the fruit fly were quickly found in mice and humans (Weber 2005, 162–64).

Now that many whole genomes have been sequenced, the genome databases and the growing protein databases serve as what

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might be called ''canned model organisms.'' These in silico data allow searches to find ''orthologous genes'' that can be traced back to a common ancestor. The number of shared genes and proteins with similar activities is surprising. Most organisms share a substantial number of molecular mechanisms or modules of mechanisms that are very ancient. Evolution appears to work by fashioning new architectures from old pieces.

When such orthologous genes are found but their function is unknown in humans, model organisms provide researchers with a unique method for finding the mechanisms in which the genes function. This method is called the ''modifier screen'' (Hariharan and Haber 2003). Random mutations are induced in the organism known to have a specific mutation in a gene of interest. The added mutations in other genes may modify the usual phenotype, thereby providing clues to the molecular mechanism in which the gene of interest is important. Many different mutants in *Drosophila* can be induced and screened to detect an effect. Genes that undergo a mutation that causes a worsening of the phenotype are called ''enhancers,'' whereas genes that cause a correction of the mutant phenotype are called ''suppressors.'' Additional genetic experiments allow the roles of the enhancers and suppressors in the mechanism of interest to be determined and orthologous genes sought to investigate the scope of the newly discovered mechanism components.

Some philosophers raised concerns about whether the use of simple model organisms might skew results, but Schaffner replied that model organisms ''are not only intended to be *representative* prototypes, but also to be 'idealized' in the sense of sharpened and more clearly delineated. The value of sharpened, simplified idealizations is a lesson that the physical sciences can still teach us. ... Once simple prototypes are preliminarily identified ... *then* variations (often in the form of a *spectrum* of mutants) are sought (or re-examined) to elucidate the operation of simple mechanisms'' (Schaffner 1998, 280; italics in original).

Thus far in molecular and neurobiology, simple model organisms have proved very useful. The extent to which simple model systems and the search for simple mechanistic accounts must be supplemented in the face of biological complexity remains to be seen (for example of failures of the mechanistic research program in the face

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of complexity, see Bechtel and Richardson 1993). Nonetheless, many types of models have proved very fruitful in the discovery of biological mechanisms.

5. REASONING STRATEGIES FOR DISCOVERY: GENERATING, TESTING, AND REVISING

Analyzing reasoning in discovery is a much more tractable task when what is to be discovered is a mechanism (rather than a vaguely characterized explanatory theory). Further, discovery is an extended process of generation, evaluation, and revision of mechanistic schemas and sketches. Model organisms and model experimental systems may play many different kinds of roles in all stages of discovery. They may be used for exploratory experimentation, prior to (or in place of) using a conceptual analogy, to discover possible components of the mechanism. In the discovery of the mechanism of protein synthesis, Paul Zamecnik and his colleagues worked to perfect an in vitro experimental system that would incorporate radioactive amino acids into polypeptides (components of proteins). They centrifuged rat livers to extract components, including microscopically visible particles (later called ''ribosomes''). They found that they had to put into the in vitro system a particular centrifuge fraction extracted from the rat livers in order to produce incorporation of amino acids into polypeptide chains. This case shows that an in vitro experimental model system can be constructed by physically decomposing an actual organism and then investigating the working parts (Rheinberger 1997). Ideally one can isolate all the mechanism components and determine their roles within the mechanism. But even before a thorough characterization is available, a running mechanism may be constructed in vitro to allow further exploratory experimentation of its parts. Such exploration is one of many ways that generation and testing are closely tied during mechanism discovery (Darden 2006, chap. 3).

More often, model organisms and model experimental systems are used to test plausible mechanistic hypotheses generated via analogy, presumed homology, or other means. Craver (2002b) detailed experimental strategies for testing a hypothesized mechanism. Such experiments have three basic elements: (i) an experimental setup in which the mechanism (or a part of it) is running, (ii) an intervention

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technique, and (iii) a detection technique. The mechanism sketch or schema being investigated may provide an abstract framework for constructing an experimental protocol: intervene here; detect there. Biologists set up many kinds of experimental models to test mechanistic hypotheses. Intact living organisms have many mechanisms running; the challenge with intact organisms is to find ways of individuating single mechanisms and ruling out confounding factors. In vitro preparations solve some problems encountered with in vivo ones. The challenge is to find the appropriate components and make them work in an in vitro experimental system.

Craver (2002b) discussed several different kinds of intervention strategies that have been used historically to test a mechanistic hypothesis in an experimental model. First are *activation strategies*, in which the mechanism is activated and then some downstream effect is detected. One example of the use of a model organism is to put a rat into a maze and detect activity in its brain cells with a recording device. A common biochemical intervention is to put in a tracer, such as a radioactive element; activate the normal mechanism; and detect the tracer as it runs through the mechanism. Good recording devices and tracers do not significantly alter the running of the activated mechanism; they merely allow observation of its workings.

Second are *modification strategies* that involve not merely activating but modifying the normal working of the mechanism operating in the model system. A way to learn about a mechanism is to break a part of it and diagnose the failure (Glennan 2005). A fruitful way to learn about the action of a gene is to knock it out and note the effects in the organism. As with the notorious ablation experiments in physiology in the nineteenth century, the problem with gene knock-out techniques in intact animals is that such a missing part may have multiple effects that are difficult to disentangle, given the often complex reactions between genotype and phenotype.

Another kind of modification strategy is an *additive strategy*. Some component in the mechanism is augmented or overstimulated, then effects are detected downstream. Craver's example was of engineered mice with more of a specific kind of neural receptor. Those mice learned faster and retained what they learned longer, thereby providing evidence for the role of such receptors in learning and memory.

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Craver (2002b) suggested using all three types of strategies – activation, ablation, and addition. Consistent results strengthen the evidence for the hypothesized mechanism. Each helps to compensate for the weaknesses of the others to yield a robust (Wimsatt 1981) conclusion, namely, a conclusion supported by a variety of types of evidence (Lloyd 1987).

In addition to manipulating an intact, operating mechanism, one may seek evidence for the existence and nature of hypothesized entities, activities, and/or modules separately. For example, an ion channel protein may be isolated and its structure investigated to find its role in a neuronal mechanism. The protein could be genetically altered to have an abnormal additional part to investigate how that affects its functioning. A positive result of such investigation of a hypothesized part of a mechanism is an example of what Elisabeth Lloyd (1987) called ''independent support for aspects of the model,'' to distinguish it from the ''outcome of the model'' (the latter is often called ''testing a prediction of the model as a whole'').

Strategies for credentialing experimental evidence, in general, are, of course, important for assessing the evidence obtained from a model organism or model experimental system. These include use of adequate controls, reproducibility of results, appropriate use of randomization, and demonstration of the adequacy of instruments, to name only a few. Finally, evidence from two or more fields further strengthens the claim that the conclusion is robust. Sometimes a single researcher uses techniques from two different fields. Sometimes researchers from different fields provide evidence for different modules of the mechanism, as did the biochemists and molecular biologists for the mechanism of protein synthesis and the working of the genetic code. The study of interfield relations by different research groups and the coordination of their results to provide evidence for a coherent picture of the mechanism is one of the many important social aspects of the collective scientific enterprise.

A description of a particular mechanism may be located in the larger matrix of biological knowledge (Morowitz 1985), which includes hierarchically organized descriptions of mechanisms in which one mechanism serves as a part of a larger one. The matrix also includes longer temporal series of mechanisms that indicate which mechanisms occur before and after a given one. These requirements for an adequate description of a mechanism constrain

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and guide mechanism discovery, as a description of each is sought, any missing components are filled, and coherence within a wider context is explored.

As we have seen, discovery of mechanisms involves generating of possible and plausible mechanistic hypotheses (e.g., by analogy or homology), testing those hypotheses in model organisms and model experimental systems, and deciding whether a newly proposed mechanism fits coherently into the matrix of other known mechanisms. Another part of the discovery process is error correcting. During testing, a failed prediction yields an empirical anomaly. The mechanistic hypothesis may be in need of revision (Wimsatt 1987). A fruitful and oft employed strategy is to overgeneralize from a successful result, use it analogically in other cases to construct plausible hypotheses, then specialize when anomalies arise. A systematic search for anomalies allows the scope of a mechanism schema to be determined. Further, anomalies guide the generation of hypotheses about alternative, variant mechanisms that do not fit the hypothesized schema.

As in the extended discovery processes of generation and testing, the view that what is to be discovered is a mechanism provides guidance in reasoning to resolve anomalies. Such reasoning in anomaly resolution is, first, a diagnostic reasoning task, and then a redesign task. The location of the failure is sought. Philosophers have been unduly pessimistic about the ability to localize the site of failure in some holistic web of beliefs. In practice, scientists often localize the erroneous part of a mechanism schema and correct it. Diagrams of the mechanism's stages aid localization of the problematic component. Then, depending on the site of localization, a redesign process may be needed to improve the hypothesized mechanism. The hypothesized mechanism or mechanism schema aids both diagnosis to localize the failure and, if required, redesign to supply an improved module.

As a first step in the anomaly resolution process, the anomalous result must be credentialed to ensure that it is not the result of an observational or experimental error. Experiments revealing an anomaly may be reproduced, using careful controls, or investigated, using other credentialing strategies for experimental results (for more on characterizing anomalies, see Elliott 2004).

Once the anomalous result is confirmed, the location of the failure needs to be diagnosed. On the basis of the extent of revision

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required, an anomaly may be categorized as a monster, special case, or model anomaly. If the anomaly can be localized outside the domain of the mechanism schema, then no revision is required. Another possibility is that the anomaly might result from a disease or other abnormality. Such ''monster'' anomalies can be barred from requiring a change in the normal mechanism schema. An example of monster barring occurred when lethal gene combinations produced anomalous genetic ratios; normally the combination of two genetic alleles does not lead to the death of the embryo. No revision in claims about normal genetic mechanisms was required with the discovery of lethals; a kind of failure had been found.

Sometimes, the anomaly requires a splitting of the domain in which the mechanism is claimed to operate. If the anomaly only occurs in a small part of the domain, the anomaly is a ''special case'' anomaly. For the small domain consisting only of retroviruses, a RNA → DNA step was added to the usual mechanism schema for protein synthesis.

In contrast to monster and special case anomalies, model anomalies indicate what is normal for a domain of wide scope. Thus, the anomaly is a model in the sense of an exemplar. There may be no sharp divide between special case and model anomalies as domains are split to accommodate variations in the ways mechanisms operate. The boundary between special case anomalies and model anomalies is not sharp.

Once the anomaly is judged to require revision of a mechanism schema, further guidance results from a diagrammatic representation of a mechanism or other means of locating its modules. In the mid-1950s, the ribosome was hypothesized to play the functional role of the template for transferring the order of the bases in the DNA to the order of the amino acids in a protein.

DNA → template RNA → protein
DNA → ribosomal template → protein

Anomalies began to accumulate for the ribosomal template hypothesis. As Douglas Allchin noted in examining other cases, presence of multiple anomalies localized in the same site of a hypothesis strengthens the confidence that revision is required. Attempting to resolve the anomaly in which the base ratios of DNA and ribosomal RNA did not correspond, Crick (1959) at

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first systematically generated alternative hypotheses to save the "ribosome as template" hypothesis. This anomaly indicated a problem about the "DNA → RNA" step in the proposed mechanism. He proposed alternatives localized in this module of the mechanism. Each component of this module served as a location for generating "how possibly" redesign hypotheses. This case shows a single researcher systematically generating a set of alternative redesign hypothesis at the site of failure.

Conservatively, the set of alternatives Crick discussed in 1959 did not include the postulation of an as yet undiscovered type of RNA having a base composition like that of DNA. This was the idea of a separate messenger RNA (mRNA), different from the known types of RNA. The discovery of such a messenger RNA was the way the anomaly was soon resolved. Tracer experiments supplied direct evidence for the existence of mRNAs. The functional requirement of a template, at that stage of the mechanism, with appropriate relations to the stages before and after it, acquired a new role filler, namely, messenger RNA (discussed in Darden 2006, chap. 3).

This ribosome anomaly case shows that when what is to be revised is a mechanism schema, that schema furnishes much guidance for anomaly resolution. Diagrams and other representations of the modules of mechanisms guide localization and redesign. When an anomaly is localized to a stage, then redesign may need to be done by adding something before or after the stage or changing hypothesized entities and/or activities within the stage itself. Furthermore, the entities and activities of a stage must give rise to the next, thereby imposing constraints on the components of a subsequent stage, on the basis of what the prior one can produce. Also, the modules of the mechanism not implicated by the anomaly must be shown to continue to function. The desideratum of having a productively continuous mechanism thus aids redesign during anomaly resolution.

In sum: reasoning in the discovery of a mechanism is guided by the description of the phenomenon of interest, aided by the characterization of what a mechanism is, and elaborated by specifying the features that an adequate description of a mechanism should satisfy. Mechanism discovery involves tight relations among generation, evaluation, and revision of mechanism schemas of varying scope. Philosophers should not view discovery as a process of floundering in

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an unconstrained space of vaguely characterized theories. If the goal is to discover a mechanism, much can now be said about reasoning strategies and experimental models to aid that task.

6. CONCLUSION

Philosophers of biology, working on cases from molecular biology, cell biology, and neurobiology, have characterized mechanisms as used in those fields. Analogue models, model organisms, and model experimental systems aid the discovery of mechanisms. Reasoning in generation, evaluation, and revision converts incomplete mechanism sketches to well-supported mechanism schemas.

This new perspective on mechanisms, arising in the philosophy of biology, allows the reexamination of traditional topics in the philosophy of science. These topics look different when one starts with mechanisms (rather than, e.g., perspectives arising from mathematical physics or formal logic). This research program is just beginning; the citations here point to recent work. Philosophers argue that appeal to mechanisms provides an account of causation (Glennan 1996, Machamer 2004, Tabery 2004, Bogen 2005), discovery (Thagard 2003, Bechtel and Abrahamsen 2005, Glennan 2005, Darden 2006), explanation (Machamer, Darden, and Craver 2000, Glennan 2002, Bechtel and Abrahamsen 2005), functional analysis (Craver 2001), interfield integration and unity (Craver 2005, Darden 2006, chap. 3), and reduction (Craver 2005, Darden 2006, chap. 4). These authors stress the importance of mechanisms in such fields as Mendelian genetics, molecular biology, cell biology, neuroscience, cognitive science, and linguistics. As yet unsolved are the issues of how this view of mechanisms applies to analyzing the mechanism of natural selection (Skipper and Millstein 2005) and to analyzing mathematical models in population genetics and ecology. Mathematical and computer simulation models of mechanisms usually have equations or functions to produce state transitions, while omitting representations of structures and the activities that produce the transitions. Could these impoverished mathematical models be improved by adding the details of the working parts of mechanisms?

This new mechanistic perspective is proving fruitful for reexaming issues in philosophy of science from the point of view of philosophy of biology. It is likely to continue to provide new insights.

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